STUDIES OF THE RENAL CIRCULATION

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TO

WILLIAM BOWMAN

(1816–1892)

CLAUDE BERNARD

(1813–1878)

RICHARD BRIGHT

(1789–1858)

FOREWORD

This book is the result of the co-operation of a clinician, a radiologist, a physiologist, and a pathologist, each making in his own way his essential contribution to a common problem. It is an example of true team-work of a kind which might with profit be more often undertaken. It describes a hitherto little used technique applicable to many fields of investigation and demonstrates the existence of a mechanism for the control of the circulation in the kidney of the rabbit which, if present in man, will certainly profoundly influence our concepts of the physiology and pathology of that organ

For me the work has had a special fascination as it illumines much on which I have long pondered. One of
emergencies is the developmen
by the pathologists as 'acute
occur in association with a wide variety of conditions such as trauma, incompatible blood transfusion, obstetric shock and accidental haemorrhage, blackwater fever, gall-bladder operations, and severe intoxications as in diphtheria, septic abortion, and gas gangrene infection. The paradox in these cases is the lack of a morbid anatomical lesion in the kidney adequate to explain the occurrence of anuria. In fatal cases all that is seen is a focal interstitial inflammatory infiltration, usually of slight degree, with some tubular epithelial necrosis. This may be accompanied by a variable amount of pigment cast formation which, though frequently advanced as an explanation of the anuria, has always seemed inadequate to the purpose. In some of the above-mentioned conditions an apparently identical disturbance of function is associated with massive cortical necrosis of the kidney with sharp delineation between the necrotic cortex and the relatively unaffected medulla. For these phenomena the occurrence of an alternative intrarenal circulation, so beautifully demonstrated by the authors, through which, when active, the blood by-passes the cortex, offers an attractive explanation

The demonstration of a vascular mechanism leading to cortical ischaemia immediately leads to speculation on its possible relation to arterial hypertension in which renal ischaemia has in recent years been shown to play a fundamental role. If renal pressor substances are responsible for the production of the malignant form of essential hypertension, a severe and prolonged renal ischaemia must be postulated and the basis of this ischaemia must be functional since, as I have repeatedly emphasised, organic vascular changes in the kidneys are minimal in the early stage. It is tempting to seek the explanation in the mechanism the authors have revealed.

The significance of their observations is not, however, confined to the kidneys Anatomical studies give reason to suppose that similar by-passes may be widely distributed in the body. The functional demonstration of such a by-pass in the kidney may now lead to a clearer understanding of their physiological significance. Indeed, it may well happen that this demonstration of rapid and extensive change in the calibre of main vessels associated with a variable by-pass regulating the site and extent of capillary activity may lead to a new concept of the circulation and its regulation

It is, therefore, with particular pleasure that I write this foreword to a study that not only throws much light on renal problems which have been my special interest, but also may well open up new concepts of vascular function in other fields.

ARTHUR W. M. ELLIS.

OXFORD,
April, 1947.

PREFACE

AMONG the many proofs of sympathy and friendship which I have received from my colleagues during the researches described in the following pages, not the least is that they have invited me to write a preface to this monograph. They have done this, they tell me, because I first conceived the possibility of the renal vessels being involved in a proximally-spreading vasoconstriction, and because the studies carried out in 1941 by Dr. J. Barnes and myself were a prelude to the present ones. I appreciate this generous gesture more than I can say.

In the following chapters we give an account of the progress of a research from its initial stage, involving the elaboration of a hypothesis, to one in which the wealth of data obtained are capable of a rational integration To me the results are a twofold cause of satisfaction In the first place, they have strengthened my belief that from the happy association of clinicians interested in research and laboratory workers medicine can acquire new powers for the conduct of original research In the second place, they have confirmed my long-standing conviction that the health or otherwise of an organ or system is ultimately dependent upon the state of its circulation It is upon this principle that the treatment of accident wounds is based, and it is also my personal belief that the great reduction in the number of gas gangrene infections during the second world war has been in large measure due to the progressive acceptance of the same principle

It is unfortunate, I think, that the great majority of centres for medical research are organised and run without the collaboration of clinicians. It is equally regrettable that clinicians so frequently attempt to solve problems by themselves without adequate knowledge and experience of the specialised methods by means of which theory can be replaced by a chain of proved facts

It has been of great good fortune to me that the Nuffield Institute for Medical Research, Oxford, holds the door open to clinicians with problems to solve The idea of this research centre, in which radiological techniques are employed as the basis of experimental studies, was due entirely to the vision of the physiologist of our team (K J. F), who brought to his aid a radiologist of long-standing experience (A. E B); the latter in his turn introduced the third collaborator of the Nuffield Institute research team (M. M L P).

To these three people Dr. Barnes and I appealed early in 1941 to ask for help in investigating the possible part played by reflex stimulation caused by trauma on the blood supply of the kidney. This request was readily granted, although at that time Miss Prichard was the only member of the team who was able to take an active part in the research. The results of this early work were encouraging, but under war conditions it was impossible to undertake more than a preliminary investigation, and it was not until the war was over that we were able to take up the research again.

In September, 1945, the work was continued, the team now consisting of Dr Franklin, Dr. Barclay, Miss Prichard, and myself. Dr. Barnes was no longer in Oxford and his valuable co-operation was not therefore available. The close collaboration of the team of four workers rendered possible a rate of progress that brought us to realise in less than three months that the blood distribution in the kidney had not the constancy which is commonly assumed, but on the contrary that it could vary. We realised at once the implications of this finding and the necessity for confirming it and for determining the channels through which the blood was diverted as an alternative to the accepted pathway. This latter need made it necessary for us to add to the team a new member (Dr. Daniel[1]) with specialised knowledge of microscopic anatomy. It thus became possible to integrate the physiological data collected from our radiological studies and from our visual observations of changes in the circulation of the kidney with the relevant anatomical findings and so to produce a more complete story

The work we took up again in 1945 is not yet finished, and the account in this book should be considered in the light of a progress report upon one section of it. We felt, however, that our researches had reached a stage at which they must be written up if we were to be in a position to survey our results as a whole, and in addition we had had many requests from those who had seen some of the work that we should publish our findings.

In the course of our work we have read, or re-read, much past literature, and our bibliography gives some idea, though it is not a complete list, of the books and papers which we have consulted With three previous workers in particular we have found ourselves in special sympathy, namely, William Bowman, who was led through structure to function; Claude Bernard, who became interested in structure through function; and Richard Bright, who was the first to appreciate the altered function and structure of the kidneys in disease. We have therefore dedicated this book to the memory of these three great men, but we have also had in mind, in so doing, all those others who

[1] *Of the Department of Pathology*, Radcliffe Infirmary, and the Nuffield Department of Surgery, University of Oxford

contributed in various measure to the sum total of knowledge which was available to us in the literature.

> 'Alguna fi en aquest món se troba;
> no és vera fi, puis que no fa l'hom fèlix.
> És lo començ per on l'altra s'acaba,
> segons lo curs que entendre pot un home.'[1]

JOSEP TRUETA.

WINGFIELD-MORRIS ORTHOPAEDIC HOSPITAL,
OXFORD.

[1] 'Whatever end man aims at in this world
is not the final end, for it gives not man full happiness
What was an end becomes a new beginning,
according to the course that man can understand'

Auziàs March (1393-1459), Catalan poet and philosopher.

ACKNOWLEDGEMENTS

WE are grateful to many people who have shown an interest in the studies which form the subject of this book. It is impossible to thank them all individually, but we should like to express our especial gratitude for the encouragement which we have received during the work from Dr. A W M. Ellis, Regius Professor of Medicine, Sir Hugh Cairns, K.B E., Nuffield Professor of Surgery, Mr. H. J Seddon, Nuffield Professor of Orthopaedic Surgery, Professor Dorothy S Russell, and Mr J. R. P O'Brien Professor Seddon has had the longest association with the research, having supported it from its origin in 1941

We gratefully acknowledge a generous grant from the Medical Research Council, which made it possible for us to develop on a larger scale the initial experimental studies To the Nuffield Foundation we must also express our thanks for their interest in and support of the work of the Institute.

For the provision of human kidneys, a study of which formed an essential part of the investigation, we are indebted to Dr. A. H T Robb-Smith. Material from cats was kindly provided by Professor E. G T. Liddell, and for the provision of dogs' kidneys we are indebted to Professor J. H. Burn and Dr E. Bülbring. To all of these we extend our thanks.

We should like also to express our gratitude to Dr. W. J. D. Fleming for help in many ways, and to the Staffs of the Radcliffe Science Library, and of the Library of the Royal Society of Medicine, and to Mr. W R. Le Fanu, Librarian of the Royal College of Surgeons, from whom we have received much assistance

We are grateful to Dr. I Doniach and Dr. A. H. C. Walker and to the *Journal of Obstetrics and Gynaecology* for permission to use the illustration reproduced as Figure 73. Figures 1 and 3 are reproduced by permission of Hamish Hamilton Medical Books and the *British Journal of Surgery* respectively, and Figures 18 and 20 *a*, *b*, by permission of the *Lancet* The diagrams reproduced as Figures 25, 28, and 54 were kindly drawn for us by Miss A. Arnott

Finally, for their technical assistance in the research, we wish to thank Mr M S Tuckey and Mr. R. Beesley, and for their contribution in the secretarial work involved we express our gratitude to Miss R Kay Shuttleworth and Miss J E Lambourn

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Preliminary Studies on Vascular Spasm

In March, 1941, while Britain was suffering heavily from air-raids, Bywaters and Beall published the first contemporary account of a post-traumatic condition which they had recognised and for which they coined the name 'crush syndrome'; they reported four cases in which the victims had died from kidney failure after having had one or more limbs crushed for several hours under fallen masonry, stones, or heavy beams

In these four cases, as in others subsequently reported, there were several features in common, including:

1. A continuous compression of one or more limbs (usually, though not invariably, the legs).
2. In most instances, temporary improvement of the patient after release from the compression.
3. Progressive impairment of kidney function until death from renal failure occurred about a week after the infliction of the injury.

The clinical picture of the syndrome became steadily clearer as more cases were recognised and reported. In some of the cases published there was not only evidence of impairment of renal function, but there were also indications of impairment of the circulation in the injured limb, such as coldness and the development of oedema and blisters, but at necropsy these cases showed neither evidence of gross damage to the main arteries nor the presence of emboli or thrombi in these vessels.

At the time it was thought by many workers that the impairment of renal function was due to damage to the kidney produced by toxic substances liberated by the crushed tissues It occurred, however, to one of us (J. T.) that the original injury might cause spasm of the main arteries of the affected limb and that this arterial spasm might extend proximally and even involve the renal arteries Such spasm of the renal arteries might lead to renal anoxia and thereby to impairment of renal function. This hypothesis was based on some published records of oliguria and even anuria noted during the course of hysterical attacks Laycock (1838), who had published reports of two such cases, was one of the first physicians to recognise the relationship between a nervous disorder and a disturbance of renal function. Somewhat later Charcot (1877), although originally sceptical of the reality of

disorder described by Laycock, found that he had to modify his opinion as a result of studying a remarkable case of what he called hysterical ischuria (a term used also by Laycock), which he investigated with great thoroughness in his wards at the Salpétrière Hospital over a period of several months. Charcot's patient had severe contractures of all four limbs, a feature which had also been observed by Laycock. From the vivid account of the case given in his lectures, it is clear that Charcot appreciated the influence of the nervous system on the output of urine.

A consideration of these and similar cases suggested that the mechanism which produced the oliguria or anuria was a nervous one, operating either directly on the kidneys themselves or on their vessels, or possibly indirectly by reflexes initiated in the contracted muscles It seemed possible that some such mechanism in which the nervous system was an important link might be brought into operation by a crushing injury.

To discover whether prolonged constriction of a limb could cause persistent spasm of its main arteries, a series of experiments was carried out by Barnes and Trueta (1942). The radiographic studies on which this research was primarily based were carried out at the Nuffield Institute for Medical Research, and the experimental technique used was suggested by the findings in a human case briefly reported by Griffiths (1940). A tourniquet had accidentally been left in position for six hours; eighteen hours after its removal, the signs of ischaemia persisting, the limb was explored and the femoral artery was found to be in a state of spasm. Accordingly, Barnes and Trueta decided to use a tourniquet as the constricting agent and to see whether in experimental animals the application of a tourniquet to one of the limbs for a period of several hours would cause persistent spasm of the main arteries in that limb. Rabbits, anaesthetised with intraperitoneal nembutal followed by open ether, were used for the research. The fur of one leg was clipped and a tourniquet, consisting of a piece of flexible wire enclosed in rubber tubing to avoid injury to the skin, was applied to the root of the thigh. Applied at this site, a tourniquet exerts pressure over the femoral vessels at a level where they lie relatively exposed in the groin. To prevent it slipping down the leg, the tourniquet was hooked over the ischial tuberosity before being tightened. The wire was tightened with pliers until the blood flow in the femoral artery was completely arrested. The tourniquet was left in position for four and a half hours; this period of time was chosen arbitrarily, but as the preliminary results were satisfactory it was adhered to throughout the research.

At various intervals after the removal of the tourniquet angiographs were made[1] of both hind limbs. The abdomen was opened, and 5 ml. of a 50 per

[1] Throughout this book the term angiograph is used to denote a radiograph which is taken after an intravascular injection of contrast medium, and in which arteries and/or veins are seen. The word 'made' is used in order to cover the two processes, namely, the injecting of the contrast medium and the taking of the radiograph.

cent solution of sodium iodide in saline were injected into the aorta through a fine needle, the injection taking from six to ten seconds. The hind limbs

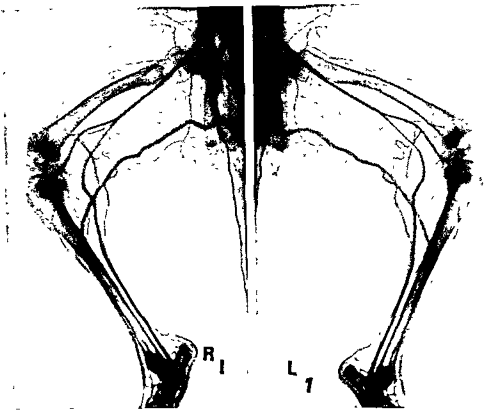

FIG 1 Angiograph showing the distribution in the normal anaesthetised rabbit of contrast medium injected, after laparotomy, into the abdominal aorta The radiographic exposure was made just before completion of the injection (The same technique was used in making the angiographs reproduced as Figures 2 to 4) The whole arterial tree of both hind limbs is well filled, and the contrast medium is returning through the veins.

were held in position over a wide-angled V-shaped support, a separate film

the pictures. A first exposure was made towards the end of the injection when 4·5 ml. had been injected; the films were then quickly changed, and a second exposure was made about ten seconds after the first.

A group of animals was used to serve as controls, no tourniquet being applied In these the whole arterial and venous tree of the two hind limbs was seen to be well filled in the first angiographs, the filling of the veins being particularly noticeable (Figure 1).

In one group of the tourniquet animals angiographs were made within an hour of the removal of the tourniquet. In every case the artery of the leg to which the tourniquet had been applied was constricted; in one animal the

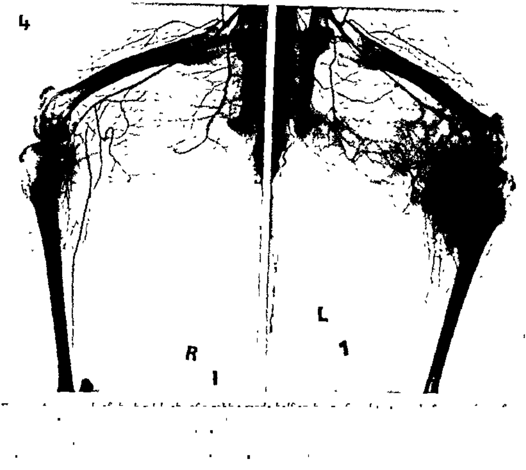

Figure 1

arterial spasm was localised, but in the rest it affected the whole femoral arterial tree below the level of the tourniquet, and the distal branches were either empty or very poorly filled. In some of the animals there was, in addition, a well marked spasm of the femoral artery of the *uninjured* limb, the spasm beginning at a level corresponding approximately with the site of the tourniquet on the other limb (Figure 2). In all these animals the veins were never seen in the first films of the serial angiographs; they were seldom seen, and then only faintly, in the second films. In one of the animals of this group not only was the arterial tree of both limbs, injured and uninjured, in a

state of spasm at and below the level of the site of the tourniquet, but the femoral artery of the injured limb was also in marked spasm *above* this level, the spasm extending to the upper limit of the film (Figure 3).

Fig 3 Angiograph made 1¼ hours after removal of a tourniquet which had been applied to the *right* thigh for a period of 4½ hours The thigh of the injured limb is markedly swollen Note the intense spasm of the femoral artery in both hind limbs below the level of the site of the tourniquet On the *right* (injured) side the spasm is seen to affect the artery *above*, as well as below, the level of the site of the tourniquet, and this spasm extends to the upper margin of the film The more peripheral vessels of both hind limbs are unfilled, and no veins are seen

In another group of rabbits angiographs were made at intervals up to seventy-two hours after the removal of the tourniquet, and these showed that the arterial spasm [illegible]

[illegible]

of the arterial tree of the affected limb, and a somewhat better but nevertheless relatively poor filling of that of the uninjured limb In neither leg is the

injected contrast medium seen to have reached the veins in this the first angiograph of the serial set, indicating a reduced circulation through both hind limbs.

FIG 4 Angiograph made 72 hours after removal of a tourniquet which had been in position on the *right* thigh for a period of 4½ hours It will be seen that even after this considerable interval since the infliction of the injury the circulation through both hind limbs is still impaired, the arterial spasm being particularly pronounced on the injured side Compare with Figures 1 to 3

These experiments showed that the prolonged constriction of a limb by a tourniquet produced in the rabbit three significant effects on the vessels:

1. A severe and persistent spasm of the arteries of the injured limb.
2. A frequent though not invariable spasm of the arteries of the uninjured limb.
3. An occasional extension of the arterial spasm proximal to the site of the injury.

Not only, therefore, had the experiments provided the answer to the immediate problem of the investigation, but they had shown that the spasm produced by the tourniquet was not necessarily limited to the arteries of the injured limb, for the arteries of the uninjured limb might be affected to an almost equivalent degree. Of still greater significance, however, was the observation that arteries proximal to the level of the constriction might be involved in the spasm. Since the constriction of one thigh could produce not only spasm of its own arteries, but also a reflex spasm of the arteries of the opposite thigh, and at the same time a spasm proximal as well as distal to the level of the constriction, it was possible that a reflex spasm might affect a considerable part of the arterial tree of the body, including the renal arteries, as had been postulated in the original hypothesis

How far the spasm might extend proximal to the level of the constriction could not be determined by means of the technique used in this series of experiments, and the next stage in the work, namely, a study of the effects which the application of a tourniquet and other experimental procedures might have on the abdominal vessels, and in particular on the renal vessels, is described in Chapter II.

CHAPTER II

Angiographic Studies, with Special Reference to the Renal Circulation

THE experiments described in Chapter I had shown that the application of a tourniquet to the thigh of a rabbit caused an arterial spasm which might extend proximal to the level of the site at which the tourniquet had been placed. The next stage of the research was to determine whether this spasm ever extended far enough to involve the arteries in the abdomen, and in particular the renal arteries.

We decided that for this series of experiments a technique of angiography must be developed which would permit the abdominal vessels to be demonstrated without opening the abdomen, and with a minimum of operative interference. The sodium iodide used as a contrast medium in the preliminary studies for demonstrating the vessels of the lower extremities was unsuitable for this investigation owing to its toxicity, and another radiopaque substance had to be selected.

For this series of experiments, as for the previous group, rabbits were used, since they were the only animals of adequate size available in sufficient number at the time. Anaesthesia was induced with intravenous nembutal, in a dosage of 0·45 ml. per kg body weight, supplemented with open ether as necessary.

Earlier studies of the circulation undertaken at the Nuffield Institute in

a similar technique could be used for demonstrating the abdominal vessels. Preliminary experiments were carried out to determine (1) the most suitable contrast medium, (2) the amount of this medium which must be injected to demonstrate the abdominal vessels with sufficient clarity to permit measurement, and (3) the proper timing of the radiographic exposures in relation to an injection of the contrast medium by the jugular vein. First tests were carried out using perabrodil (diodrast), an iodine compound which is excreted by the kidneys and which, therefore, might have been used for the dual purpose of demonstrating the blood flow to and from the kidney and of studying renal excretion. In the 35 per cent solution, however, which previous work had shown to be well tolerated by experimental animals, the contrast was insufficient for satisfactorily demonstrating the renal blood vessels,

and in a solution of 70 per cent this substance, while providing good contrast, was found to cause a marked fall of blood pressure (Figure 5*a*), which contra-

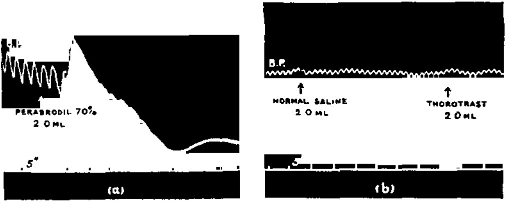

FIG 5 Records of arterial blood pressure in two rabbits showing (*a*) the fall produced by an intravenous injection of perabrodil in a concentration of 70 per cent, and (*b*) the absence of effect following a similar injection of thorotrast

indicated its use In view of the need of a medium of maximum radiopacity for the adequate visualisation of vessels so far distant from the site of injection, we turned to thorotrast, a colloidal substance containing 25 per cent of thorium dioxide This provided excellent contrast and was found to have no effect on blood pressure (Figure 5*b*). Thorotrast, however, is not excreted by the kidneys but is eliminated from the blood stream by the reticulo-endothelial system, especially by that part of the system which is located in the spleen[1] and liver; hence, with this contrast medium, our observations concerning the kidney were limited to the blood vessels. For a radiographic study of renal excretion another series of experiments, with contrast medium appropriate for this purpose, had to be undertaken, but this work is still far from complete

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including the renal arteries The ventro-dorsal projection, with the rabbit lying on its back, proved to be the most satisfactory for showing the renal arteries and veins, and was for this reason generally used, though lateral films were occasionally found useful as they provide a better picture of the aorta, which in the ventro-dorsal projection overlies the vertebral column.

Preliminary films were made by direct cineradiography (Barclay, Franklin,

[1] The particularly dense shadow of the spleen above the left kidney is a striking feature in many of the angiographs which are reproduced in this chapter, and is due to the concentration in this organ of thorotrast injected at earlier stages in the experiments (see Figures 10*b*, 11, 12*b*, 14, 15*b*, *d*, and 30*a*)

and Prichard, 1944, p. 37), at a recording rate of 200 frames per minute (3·3 frames per second), to determine the times taken by the contrast medium to pass from the site of injection to the renal artery and vein respectively and also the times of their optimum shadows. We found that the renal artery was best seen three seconds from the moment of injection, and that the best time for visualising the renal vein was from three to four seconds later. After prolonged anaesthesia or operative procedures these times tended to be very slightly longer. Having thus determined the times of appearance of the renal vessels, we were able to record by means of two single films, exposed at the appropriate times in relation to the injection, the shadows of the renal arteries and veins. Straightforward serial radiography, with separate films, was used for the majority of this series of experiments in preference to direct cineradiography, because it permitted a much larger field to be studied, better definition to be obtained and, last but not least, because it involved much less expenditure of film. The films used (size 15 inches by 6 inches) covered an area extending from the upper part of the thorax to the lower part of the thighs (see Figures 6, 12, and 13). In view of the extension of our field of observation from the small area (5 inches by 5 inches) of the direct cineradiographic films, the quantity of thorotrast injected was doubled, and the time of the arterial exposure was delayed by half a second to permit the filling of the more distal vessels. In many cases a third film was exposed three or four seconds after the second film to provide data about veins, particularly those of the extremities, which are seen better at this later stage

The animal was positioned on a thin wooden board with a tunnel for the film-cassettes beneath, and a metronome was used to tick the seconds. Three workers were needed, one to make the injection, another to change the cassettes and the third to operate the X-ray set, and it was a great help to have a fourth person for general assistance. Good team work, practice, and above all concentration of attention, were essential for making a rapid serial set of angiographs.

In each animal control angiographs, such as those illustrated in Figure 6, were made after anaesthesia had been induced but before any experimental procedures had been carried out. These films served as the animal's own normal, and were compared with the subsequent angiographs made after the trauma had been inflicted or other experimental procedures had been carried out. A close study of the films was made, and the calibres of the vessels, as shown by the contrast medium, were measured with an instrument specially adapted for the purpose. A pair of engineers' calipers, operated by thumb-screw and fitted with a vernier scale, had two small rectangular strips of transparent X-ray film attached to the jaws in such a way that the strips would lie flat on the radiograph. A stop was incorporated at the new closing point

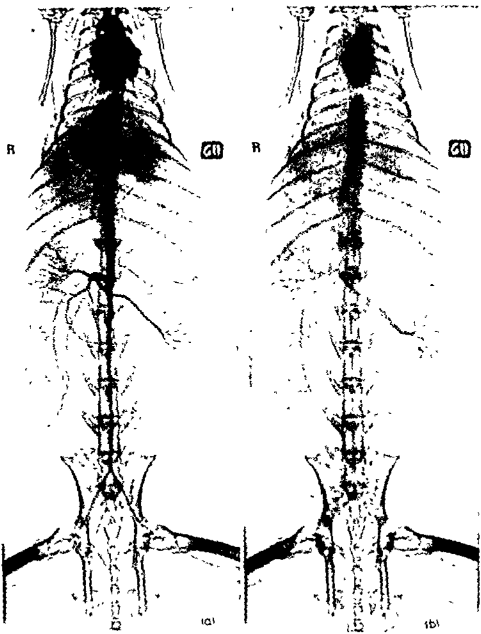


FIG. 6. Serial pair of angiographs of a normal rabbit, showing the thorotrast (a) in the arterial and (b) in the venous system. The radiographs (a) and (b) were exposed 3½ and 6 seconds respectively after the moment of the injection of contrast medium into the jugular vein. A similar technique was used in making all angiographs reproduced in subsequent figures, although the times when the radiographic exposures were made were occasionally altered to meet special conditions. The position of the vessels studied in the investigations described in this chapter is indicated in the diagram reproduced as Figure 7.

to prevent damage to these extensions of the jaws. Measurements were made from the original radiographs, viewed by transmitted light. The free

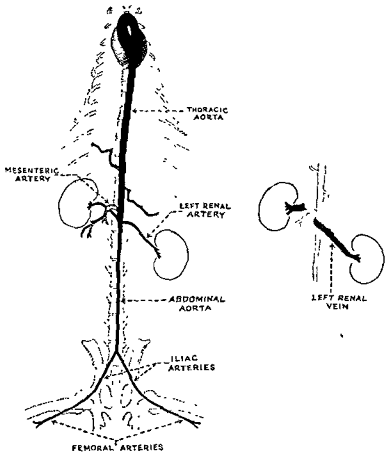


FIG. 7 Key to Figure 6 This diagram shows the position of the vessels studied in the experiments described in this chapter Note in particular the positions of the left renal artery and left renal vein

edges of the two strips of film were aligned on the outer margins of the shadow of the vessel and the reading on the scale was noted. After some practice with this instrument we found that we could determine the calibre of a vessel with a very small margin of error, as shown by the consistency of measurements when repeated on several occasions. The cross-sectional areas of the vessels, calculated from the measurements of their calibres on the assumption that the lumen in each case was circular, were used in the assessment of the results. These areas, of course, were not absolutely precise, partly because of the above-mentioned assumption and partly because of the increase, produced by squaring, in any error present in the original measurement.

They served, however, as a general indication of the degree of vascular change.

The number of animals used in some of the groups of experiments was small, and on occasion it was insufficient to prove that a given result was necessarily due to a specific experimental procedure. Nevertheless, each series of experiments, though imperfect for statistical purposes, led us step by

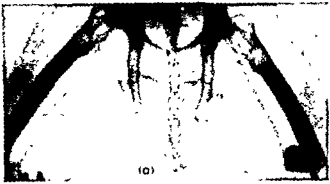


FIG. 6. Angiographs showing the reduction in calibre of the femoral artery of the *uninjured* limb which is often seen while a tourniquet is in position on the opposite thigh (*a*) before application of the tourniquet, and (*b*), same animal, after the tourniquet had been in position for 4 hours

step to a series of observations of unequivocal character. We therefore describe them to show the stages by which we proceeded to our ultimate findings. Certain other features of the renal circulation were demonstrated in the angiographs of this series of experiments, but in view of their special character they are described in later chapters where, in the light of findings made in the later stages of the investigation, their significance will be more fully appreciated

We found it advantageous from the outset to concentrate our attention

mainly on the vessels of the *left* kidney, because these vessels are longer, more easily seen and more readily accessible than those of the right kidney. For

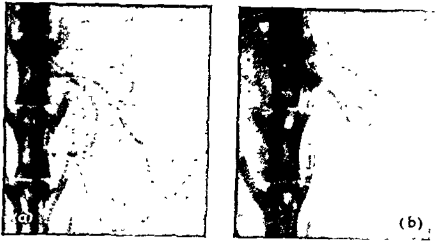


FIG 9 Angiographs showing a reduction in calibre of the left renal artery caused by the application of a tourniquet to the left thigh (*a*) before application of the tourniquet, and (*b*) 1 hour after the tourniquet had been applied and while it was still in position

the experiments summarised in the present and subsequent chapters, therefore, all procedures involving the use of tourniquets or of nervous stimulation were carried out on the left side of the animal and observations were made *primarily on the left kidney*.

The new angiographic technique having been established, it was used first for a series of *tourniquet experiments* A tourniquet, similar to that used in the experiments described in Chapter I, was applied to the left thigh for a period of four and a half hours. Angiographs were made at various times both during the period while the tourniquet was in position and also up to two hours after its removal.

The results showed that there was a general constriction of the arteries while the tourniquet was in position and that this constriction was increased after its removal. The degree of diminution in calibre varied with the different vessels: the decrease was most marked in the femoral arteries (Figure 8), next in the abdominal aorta, and then in the renal artery (Figures 9 and 10). The mesenteric artery, on the other hand, remained normal in calibre or showed even a slight dilatation (Figure 10) and the renal vein showed very frequently a dilatation of considerable degree (Figure 11).

The individual sensitivity of each animal to the tourniquet was reflected *in the variable extent to which* the calibres of the vessels were altered. In a few animals the cross-section of the renal artery showed little or no change,

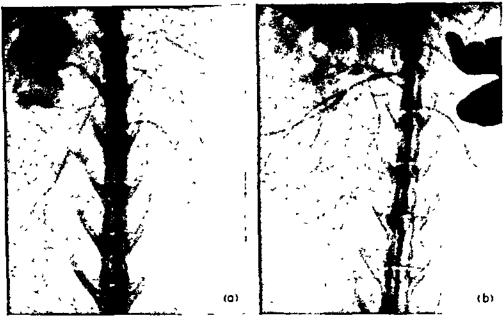


Fig. 10. Angiographs of a rabbit to whose left thigh a tourniquet was applied for a period of 4½ hours. (*a*) before application of the tourniquet, and (*b*) 70 minutes after its removal. Note in (*b*) the reduced calibres of the aorta and left renal artery, and by contrast the dilatation of the mesenteric artery. (The thorotrast injected for making angiographs at earlier stages in the experiment has been taken up by the spleen, which consequently casts the dense shadow seen towards the top right hand corner of *b*.)

Fig. 11. Angiographs showing the marked dilatation of the left renal vein which is frequently seen in tourniquet animals. (*a*) control venous angiograph, showing the calibre of the renal vein before application of the tourniquet[1]. (*b*) venous angiograph made 80 minutes after removal of the tourniquet, which had been in position on the left thigh for 4½ hours.

[1] The film shown here as (*a*) belongs actually to the second serial set of angiographs of this experiment. It has been used here in place of the venous angiograph of the control serial set because the latter was less suitable for reproduction. The calibre of the renal vein was the same in both angiographs.

but in the great majority it was substantially decreased, both during the period while the tourniquet was in position and also after it had been removed.

Our findings, therefore, confirmed the suggestion provided by the earlier series of experiments that arterial spasm, resulting from the prolonged application of a tourniquet, might extend proximally to affect the renal artery.

In view, however, of the fact that the tourniquet experiment involved at least five hours of general anaesthesia, it was necessary to determine whether the factor of *prolonged anaesthesia* in itself caused a change in the calibre of the vessels. A group of rabbits was anaesthetised in the same way as the tourniquet animals and angiographs were made at the beginning of anaesthesia and at various intervals up to six hours from the time when the anaesthesia began. Although the vessels occasionally showed a difference in calibre after prolonged anaesthesia, this difference was relatively slight by comparison with that seen in animals which had had both prolonged anaesthesia and the application of a tourniquet; moreover, it was less marked in the renal arteries than in other arteries. Figure 12 shows how negligible might be this change in calibre.

From these two groups of experiments we concluded, firstly, that a marked constriction of the renal artery might occur in anaesthetised rabbits after a tourniquet had been applied to one thigh and, secondly, that the part played by the anaesthesia in causing this constriction was at most slight.

There was one other feature in the angiographs of the tourniquet animals to which reference should be made. The shadows of the vessels were seen to become increasingly dense after each successive injection of contrast medium, particularly the shadow of the renal vein, the increased density of which appeared to be greater than could be explained by the increased calibre of this vessel. The various possible interpretations of this finding have not yet been fully considered and require further investigation.

The next step in the investigation was to determine whether the alterations in calibre of the renal vessels were the specific effects of the application of the tourniquet to the limb, or whether they were merely the results of a fall in arterial blood pressure.

We found that the only reliable method of recording the rabbit's blood pressure was the standard laboratory technique, in which a mercury manometer is connected to a cannula in the carotid artery. This method, however, could not conveniently be used to record changes in blood pressure over a period as long as five or six hours when angiographs had to be made at intervals; consequently, changes in blood pressure in our tourniquet animals were not recorded.

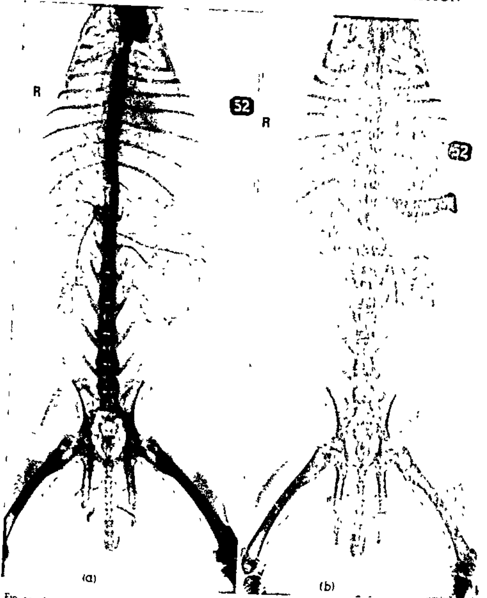


Fig. 12 App[illegible]
no appreciable [illegible]
angiograph m[illegible]
of continuous a[illegible]

To determine what effect a *raised or lowered blood pressure* has on the calibre of the vessels, and in particular on the renal vessels, we used several drugs which were known to cause an alteration in blood pressure, and made a number of angiographs simultaneously with the recording of blood pressure on a smoked drum.

The first drug to be used for this purpose was adrenaline hydrochloride. When the mercury manometer had been connected to the carotid artery and the tracing of the blood pressure had started, control arterial and venous angiographs were made. Ten to fifteen minutes later, adrenaline was injected intravenously in a massive dose intended to produce a marked effect (the dosage ranged from 0·1 to 0·17 mg. per kg. body weight). As soon as the rise of blood pressure had reached its peak a second serial set of angiographs was made. A third set of angiographs was made when the blood pressure had completed the fall which followed the initial rise. Records were thus obtained of the calibre of the vessels both under normal conditions and also when the blood pressure had been raised and lowered by a known amount.

The angiographs made when the blood pressure had been raised to its maximum (rises ranging from 34 to 54 mm. Hg.) showed a consistent picture in all cases. The renal and femoral arteries showed an intense *constriction*, while in striking contrast the aorta showed a marked *dilatation* in both its thoracic and upper abdominal segments, where at some levels its cross-section was more than twice its normal value. The renal vein showed a marked constriction.

With the subsequent fall in blood pressure (falls ranging from 10 to 47 mm. Hg. below the normal starting levels), a less consistent effect was seen. For example, one rabbit, with a fall in blood pressure to 10 mm. Hg. below its normal level, showed a slight dilatation of the lower thoracic aorta, whereas another animal, with a fall in blood pressure to 47 mm. Hg. below its normal level, showed this part of the aorta to be of normal calibre. In these same animals the renal artery showed a constriction in each case, but the constriction was more marked in the animal which showed the greater fall in blood pressure

As regards the renal vein and mesenteric artery, the results were more consistent throughout the experiment; in every animal, irrespective of whether the blood pressure was raised or lowered, the renal vein showed a definite constriction and the mesenteric artery a marked dilatation.

The most spectacular feature of the angiographs of these animals was the great increase in the size of the aorta which, at the peak of the rise of blood pressure, showed not only a very marked increase in calibre, but also a considerable extension in length, which gave the vessel a tortuous appearance (see Figure 13).

Our experiments with adrenaline seemed to us to indicate that the changes

FIG. 13. Arterial angiographs, made with the rabbit in the lateral position, showing the effects produced by an intravenous injection of adrenaline hydrochloride in high dosage. (*a*) control angiograph, made before injection of adrenaline, this film was exposed 4 seconds after the injection of contrast medium. (*b*) angiograph made 48 seconds after injection of adrenaline, when the rabbit's blood pressure was 54 mm. Hg. above its normal level, this film was exposed 18 seconds after the injection of the contrast medium. Note the dilatation of the heart and the great increase in calibre of the thoracic and upper abdominal segments of the aorta. The tortuosity of the thoracic aorta, due to increase in its length, is also striking. The intense peripheral vasoconstriction has prevented this second injection of contrast medium from reaching the distal aorta, the iliac, and femoral arteries. The great diminution in the shadows of the kidneys will be appreciated by comparison with the control angiograph (*a*).

in calibre of the renal vessels were unrelated to the level of the blood pressure, since a marked constriction of these vessels had been noted both when the blood pressure was raised to its maximum and also when it had fallen to its minimum. It appeared more likely that the constriction of these vessels was dependent on some specific action of the adrenaline rather than on any changes in blood pressure

Another drug used in this series of experiments was pilocarpine nitrate. Angiographs of a rabbit made when the depressor effect of this drug was fully operative (blood pressure reduced by 24 mm. Hg. from its normal level) showed that, while the aorta was markedly constricted, the calibre of the renal artery was within normal limits, and that of the renal vein was substantially increased. At the time of the subsequent blood pressure rise to above the original normal level, the renal vessels were of the same calibre as in the depressor stage but the aorta, while still constricted, showed a calibre more nearly that in the control angiograph. Thus with pilocarpine, as with adrenaline, the altered levels of blood pressure appeared to play no part in determining the calibres of the renal vessels.

One further observation is of interest We produced a fall in blood pressure of 34 mm. Hg. in one animal by administering amyl nitrite by inhalation. While the aorta showed a marked constriction throughout its length at this stage, the renal artery showed a definite dilatation.

This group of experiments satisfied us that a constriction of the renal artery did not necessarily coincide with a fall in arterial blood pressure, and inclined us to the view that the diminished calibre of this vessel, which had been an almost invariable feature in our tourniquet experiments, was due to a cause other than a marked hypotension.

The next experiments undertaken were designed to determine the effect of a *decrease in blood volume* on the calibres of the vessels, and particularly of the renal artery and vein. Under nembutal and ether anaesthesia, several rabbits were bled in quick successive stages until finally about a third of their total blood volume had been withdrawn. Angiographs were made immediately after each bleeding, and the calibres of the vessels were correlated at each stage with the known amount of blood which had been removed. The results showed a general constriction of all the vessels, including the renal arteries and veins *and* the mesenteric artery, proportional to the amount of blood withdrawn (Figure 14). Such similarity in response of the renal and the mesenteric arteries had not been observed in any previous group of experiments.

The angiographic picture seen after haemorrhage did not, therefore, correspond with that seen in our tourniquet animals, for in the latter the

mesenteric artery showed a normal or even a slightly increased calibre, and the renal vein was often dilated to a remarkable degree.

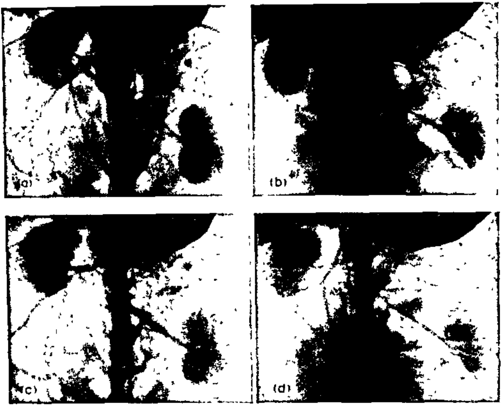


FIG. 14. Angiographs showing the effect on the abdominal vessels produced by severe, rapid haemorrhage. (*a*) and (*c*) serial angiographs showing arteries and veins respectively before haemorrhage. (*b*) and (*d*) serial angiographs showing arteries and veins respectively after haemorrhage.

In (*b*) and (*d*) the reduced calibres of the renal vessels are clearly seen. Note also the reduction in calibre of the mesenteric vessels.

Having failed to reproduce the picture shown by the tourniquet animals in any of the experiments so far undertaken, we tried to see if we could achieve our object by *stimulation of different types of nerves* by various means. We selected the sciatic nerve as the first to be stimulated, since this nerve is easily accessible and is, moreover, the main mixed nerve of the extremity to which the tourniquet had been applied in the experiments described earlier in this chapter.

Under the same anaesthesia as before, the left sciatic nerve was exposed, ligated, and then divided distally to the ligature. In some animals the central

end of the cut nerve was stimulated by clamping it with a pair of artery forceps; in others bi-polar faradic stimulation was applied for a period of two minutes. Angiographs were made at various times ranging from one and a half minutes to one and a half hours after the conclusion of the stimulation. Some of these angiographs corresponded closely with those of the tourniquet animals, showing a marked reduction in the calibre of the renal artery and a dilatation of the renal vein; the aorta, the mesenteric, and femoral arteries also showed changes in calibre similar to those seen in the tourniquet animals. These findings were not, however, constant in all animals, and the lack of uniformity in the results suggested that the response to the stimulation varied considerably with the individual subject.

In those animals in which the renal artery was seen to become constricted after stimulation of the central end of the divided sciatic nerve, this effect was interpreted as a reflex reaction due to afferent impulses travelling up the

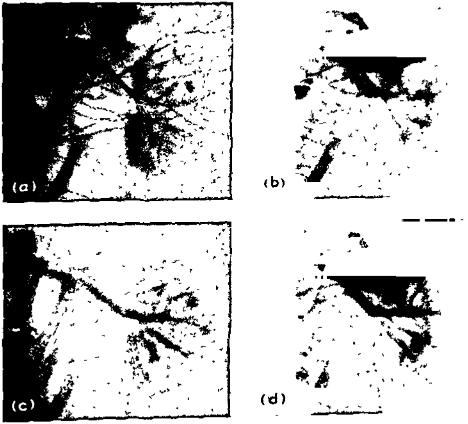


Fig. 15. Angiographs showing reduction in calibre of the left renal artery and dilatation of the left renal ... (a) and (c)

injured nerve and reaching the artery by an efferent pathway located in the splanchnic nerves. Accordingly we subjected another animal, after laparotomy, to faradic stimulation of the left splanchnic nerve for two minutes. Angiographs were made at various times from three minutes to two and a half hours after stimulation, and some of these angiographs gave pictures closely comparable with those seen in angiographs made after the application of a tourniquet, or after effective sciatic stimulation; in fact, in the angiographs made after splanchnic stimulation (Figure 15) the constriction of the renal artery was even more marked than that seen in either of these two types of experiment.

The results of all the various groups of experiments that have been described had provided an increasing body of facts which favoured our original hypothesis that the blood supply of the kidney can be reduced by a constriction of the renal artery through the intermediation of the nervous system in response to various stimuli.

To put the hypothesis to a conclusive test we decided to see whether *section of the splanchnic nerves* would prevent the reflex response of the renal vessels to the application of a tourniquet

The splanchnic nerves of several rabbits were divided bilaterally, and a period of five weeks was allowed to elapse so that degeneration might occur in the nerves and their terminations. Then, under nembutal and ether anaesthesia, a tourniquet was applied to the left thigh in the usual way and the customary number of serial sets of angiographs was made.

The control angiographs, made immediately before the tourniquet was applied, showed some striking features. The calibres both of the renal vessels and of the mesenteric artery were remarkably large when compared with the calibres of the other vessels of the arterial tree, the renal arteries being wider even than the iliac arteries, a picture just the opposite of that usually seen in the normal animal (Figure 16).

In the angiographs made while the tourniquet was in position and after its removal, all the vessels presented an appearance typical of that shown in a tourniquet experiment, *with the exception of the mesenteric artery and the renal vessels*, these showed a very slight degree of constriction, but were almost unaffected. Consequently, the calibres of the mesenteric and renal arteries were now still larger in proportion to the calibres of the other vessels than they had been in the control angiographs.

It will thus be seen that by section of the splanchnic nerves we were able to prevent the marked constriction of the renal artery which we found to occur in tourniquet animals with their splanchnic nerves intact. How effective the denervation had been was shown not only by the minimal degree

of constriction which occurred in the renal artery after the tourniquet had been applied, but to even better advantage by a comparison of this minimal constriction of the renal artery with the marked constriction of the arteries supplying the hind extremities.

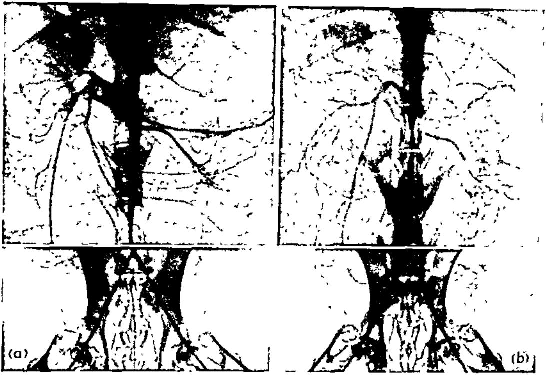


FIG 16 Angiographs to show the dilatation of the renal and mesenteric arteries which occurs after bilateral division of the splanchnic nerves (a) angiograph of rabbit whose splanchnic nerves had been divided 5 weeks previously, (b) angiograph of rabbit with splanchnic nerves intact, for comparison Note in (a) the large calibre of the renal and mesenteric arteries of the denervated animal It will be seen that the left renal artery is of even larger calibre than the iliac arteries, a picture the reverse of that seen in the normal animal (b).

In these experiments, in which a tourniquet was applied after splanchnic denervation, we found for the first time that the renal and femoral arteries responded to an experimental procedure in a divergent manner, in striking contrast to their strictly parallel response to experimental procedures in all the other groups of experiments.

We had previously been impressed by the closely parallel behaviour of the arteries which supply the kidneys and those which supply the hind limbs, and by the opposite behaviour of the artery which supplies the intestines, the mesenteric artery (whose response was parallel to those of the renal and femoral arteries in the haemorrhage experiments alone). This finding is of greater interest in view of the embryological derivation of the tissues of these parts of the body. Both the kidneys and the limbs are derived essentially

from mesoderm, whilst the other abdominal viscera are derived essentially from endoderm.

In the course of all these experiments we had made certain other observations which changed the focus of our interest from the renal artery and vein to the circulation within the kidney itself. One of these observations is described in this chapter since it was made directly from our angiographic studies; an account of others is given in Chapter III.

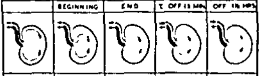
As has already been explained, when making the angiographs we exposed two separate films, carefully timed so that they would show the contrast medium in the renal artery and the renal vein respectively. In the angiographs of the tourniquet animals we noticed that occasionally, after the tourniquet had been applied, although the renal artery and vein were seen, as they usually are seen, in the arterial and venous angiographs respectively, the arterial angiograph showed a certain amount of contrast medium to be present also in the renal vein. In some cases the shadow seen in the vein may have been due to a residue from an earlier injection, but in others this explanation seemed improbable. We were surprised by this observation as it seemed to indicate that the contrast medium was taking less time than usual to pass from the renal artery through the kidney to the renal vein.

To investigate this point more accurately, angiographs of one rabbit were made by direct cineradiography, with a speed of recording of 200 frames per minute (3·3 frames per second) The result of this experiment is shown in Figure 17, where it will be seen that the time interval between the first appearance of the contrast medium in the renal artery and its first appearance in the renal vein was definitely shorter after the tourniquet had been applied than it was in the control angiographic record. The interval was decreased still more after the tourniquet had been removed. Simultaneously with this decrease in the intrarenal circuit time the

TOURNIQUET EXPERIMENT

RABBIT

RENAL CIRCUIT TIMES				
BEFORE	DURING T ON 4½ HRS		AFTER	
	BEGINNING	END	T OFF 15 MIN	OFF 18 HRS



2·7 SEC	1·8 SEC	2·1 SEC	1·5 SEC	1·65 SEC
100%	67%	78%	55%	61%

CROSS SECTION OF RENAL VESSELS				
ARTERY 100%	87%	75%	75%	81%
VEIN 100%	46%	150%	176%	160%

DETERMINED FROM DIRECT CINERADIOGRAPHIC RECORDS

FIG 17 Table based on measurements taken from direct cineradiographic record of one of the tourniquet animals (*T*, tourniquet). This shows the reduction of the renal circuit time of the injected contrast medium which was observed after application of the tourniquet (see text) This reduction coincided with a decrease in calibre of the renal artery and an increase in that of the renal vein. It will be noted that all these changes were apparent both while the tourniquet was in position and also after its removal The relatively slight variations in the renal circuit time recorded after the application of the tourniquet are probably not of significance

films showed the characteristic features of the tourniquet experiments, namely, a diminution in calibre of the renal artery and a dilatation of the renal vein.

The result of this experiment, carried out with a technique permitting accurate timing of the radiographic exposures, thus confirmed our previous suspicions that after the application of a tourniquet the intrarenal circuit time might sometimes be noticeably reduced. At the same time, the renal artery showed a marked reduction in calibre, which suggested to us that the flow of contrast medium (that is, the blood flow) reaching the kidney was reduced in volume. We concluded, therefore, that the more rapid appearance of the contrast medium in the renal vein, at a time of reduced arterial inflow, was due to the fact that in its passage through the kidney the head of the column of contrast medium was taking a shorter course than it had taken before the tourniquet was applied.

It was this observation, *made in intact animals,* which first suggested to us that a short-circuiting of the blood flow might occur in the rabbit's kidney.[1] We had as yet no idea as to where in the kidney this short-circuiting was taking place, but we realised the possible implications of an altered course of blood flow, and for the next stages of the work we diverted our attention from a study of the vessels by which the blood enters and leaves the kidney to an investigation of the circulation within the kidney itself.

[illegible] that a diminished [illegible] the resistance of [illegible] unchanged or [illegible] servations, since [illegible] nism within the kidney

CHAPTER III

Preliminary Studies of the Intrarenal Circulation

THE observations which above all others directed our attention from a study of the renal artery and vein to that of the circulation within the kidney itself were obtained from an experiment which was designed as an angiographic study similar to those described in the previous chapter. Since these observations, which had been obtained by the use of an injected dye after the usual series of angiographs had been made, led us to continue our researches by means of other approaches, they are described as the starting-point of the next stage of the work.

The primary object of the experiment had been to record the effects, on the renal vessels, of another type of nervous stimulation. Faradic stimulation of the central end of the divided sciatic nerve had shown results which approximated to those seen in our tourniquet animals more closely than the results of any other procedures. The stimulation had, however, been limited to a single application for a short period. In an attempt to reproduce the tourniquet picture even more closely, we decided to stimulate the same nerve at repeated intervals over a period of time equal to that during which the tourniquet was in position.

After the usual anaesthetics had been given, the left sciatic nerve was exposed and divided as in the previous experiments, and faradic stimulation was applied to the central end for a few seconds every fifteen minutes over a total period of four and a half hours. Angiographs were made before, during, and after this period. The results of these were inconclusive, and before sacrificing the animal we decided to see what information could be acquired, first by direct observation of the kidney and its vessels, and then by the injection of a dye into the renal artery. A laparotomy was performed and, with the left kidney exposed, the central end of the left sciatic nerve was stimulated, first faradically and later by being crushed with artery forceps. During this part of the experiment atropine sulphate was given by intravenous injection (in a dosage of 1·7 mg. per kg. body weight) so that we might observe the effect of this drug upon the renal vessels. Finally, an injection of 0·5 ml. of a 5 per cent solution of methylene blue was made through a hypodermic needle into the left and right renal arteries in turn.

We were wholly unprepared for the dramatic result which we now obtained from an experiment which up to this point had appeared unfruitful. The tw

kidneys showed a striking contrast in the distribution of the dye (Figure 18). Whereas the left kidney (the kidney on the stimulated side) showed only a

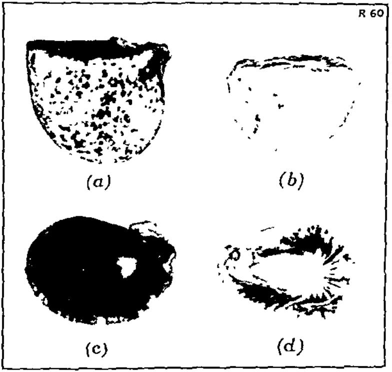


FIG. 18 Photographs of half of the right kidney (*a*) and (*c*) and of half of the left kidney (*b*) and (*d*) of a rabbit, after intra-arterial injections of 5 per cent methylene blue solution To show the reflex effects upon the left kidney of stimulation of the central end of the divided left sciatic nerve (for further description see text) Note the considerable staining of the outer

very few isolated spots of blue on its surface, the right kidney (the kidney on the unstimulated side) was irregularly stained with the dye over its entire surface. When the kidneys were sectioned radially the contrast was even more remarkable, for the cut surface of the right kidney showed an intense diffuse staining throughout cortex and medulla, whereas that of the left kidney showed the staining to be confined to the deepest layer of the cortex and to the subcortical zone of the medulla.[1]

The dye had been seen leaving each kidney by the renal vein and, as in the

[1] The unilateral effect of the stimulation in this experiment is striking, but it should not be inferred that in this respect the result of this experiment necessarily differed from those described in the previous chapter As we have already pointed out, it is more difficult in angiographs to assess changes in the circulation of the right kidney than of the left, and consequently we have not as yet attempted to determine by means of angiographic studies how often changes in the renal circulation resulting from unilateral trauma are confined to one kidney, and how often they affect both

left kidney the above-mentioned region was well stained whilst all the rest of the renal substance remained unstained, we had here the first clue to the site of the short-circuit, the existence of which we had suspected from some of the previous angiographic studies.

This experiment which, as we have already said, formed a springboard for a new approach to the whole problem of changes in the circulation of the kidney, had provided certain basic information. Firstly, it had confirmed the existence of a short-circuiting mechanism in the kidney. Secondly, it had given us a clue as to where in the kidney the short-circuiting takes place. Thirdly, it had shown that the short-circuiting mechanism could be brought into operation by a neurovascular reflex. Notwithstanding the fact that atropine had been injected during the experiment, we felt justified in attributing the short-circuiting that had been demonstrated by the dye to the agency of a neurovascular reflex, since this short-circuiting had been seen to occur only in the kidney of the left side, the side on which the nerve had been stimulated. The possibility that the atropine had contributed to the operation of the short-circuiting mechanism by contracting the vessels had, however, to be investigated. Accordingly, two experiments were carried out on exactly similar lines but without the administration of the drug. In one case (Figure 19) the result was essentially the same, the cortex of the kidney on the stimulated side remaining unstained except in its deepest zone, as in the previous experiment. In the case of the other animal the phenomenon was not repeated, suggesting that there are individual variations in response to central sciatic nerve stimulation.

FIG. 19. Print enlarged from a small coloured photograph of the left kidney of a rabbit, sectioned in the coronal plane. As in the specimens depicted in Figure 18, methylene blue had been injected intra-arterially after stimulation of the central end of the divided left sciatic nerve. Note the absence of staining in the peripheral and greater part of the cortex and the staining of the medulla to a variable depth (compare with Figure 18*d*).

The first experiments in which direct observations were made of the exposed kidney showed that useful information could be obtained from watching the colour of the surface of the kidney and that of the blood in the renal vein. Under certain conditions we saw that the surface of the kidney paled and that, while the kidney was pale, red blood might appear in the renal vein. This red blood would sometimes be seen in the form of one or

more streamlines, in marked contrast to the bluer blood of the remainder of the flow. At other times all the blood visible in the renal vein would be red.

The variability of the colour of the blood in the renal vein, which was sometimes seen before any procedure other than the laparotomy had been carried out, indicated that the blood passing through the kidney had retained a varied content of oxygen. In the light of our recent findings that the renal blood might be diverted from the cortex through a medullary pathway, the fact that red blood might appear in the renal vein at a time when the surface of the kidney was pale had a special significance, and a possible explanation of the unreduced state of the venous blood became apparent. A diversion of the blood from the cortex, the most active part of the kidney, to the medullary pathway, with a possibly increased speed of flow through these channels, seemed to us a logical explanation of the phenomenon.

Claude Bernard (1858, *a*, *b*) appears to have been the first person to describe the presence of red blood in the renal vein, and his observations were later confirmed by his pupil Vulpian (1875) and other workers. Little interest seems to have been taken in this phenomenon in subsequent years until in 1936 Franklin and McLachlin demonstrated red streamlines in the renal and other veins. A discussion of streamlining in veins in general and of red streamlines in particular, together with further references, is given by Franklin (1937).

The interpretation which Bernard gave to the appearance of red blood in a vein was supported by a number of observations made on the kidney, but it appears to have been based primarily on his studies of the circulation in the submaxillary gland. It is for this reason that Bernard's interpretation of the phenomenon, when it occurs in the blood of the renal vein, cannot be fully accepted in the light of our present knowledge. For Bernard supposed that the appearance of red blood in a vein always indicated a dilatation of the capillaries and, unaware of the existence of an alternative intrarenal pathway, he related the presence of red blood in the renal vein to the formation of urine, as he had related a similar appearance in the submaxillary vein to the formation of saliva. However, careful examination of the protocols of his experiments on the kidney (Bernard, 1859) shows a number of results which fail to support his interpretation that red blood in the renal vein is always associated with urine formation.

The results of those of Bernard's experiments in which red blood was seen in the renal vein at a time when no urine was being formed find a probable explanation in the light of our own observations. In these cases we suggest that the absence of urine formation when the colour of the venous blood was red was due *either* to the fact that the blood had been diverted from the cortex and had passed through the medullary pathway in a manner

similar to that which we have ourselves demonstrated, *or* to a diminished glomerular pressure due to an intense general and local vasodilatation, an interpretation which is based on several of our observations.

On the assumption that red blood appearing in the renal vein at a time when the surface of the kidney was pale indicated that the intrarenal blood had been short-circuited through the medulla and had by-passed the cortex, we carried out a series of experiments to try to discover under what conditions this short-circuiting mechanism could be brought into operation. These experiments may conveniently be divided into two main groups: those in which a drug was administered, and those in which stimulation was applied. In some experiments an intravascular injection of a radiopaque or other substance was made to provide a permanent record.

It will be noticed that in certain cases the records of our findings are incomplete and do not cover all the observable phenomena The reason for this is that in many instances the experiment was designed for the elucidation of a single point. It was only in the case of experiments which were either repeated a sufficient number of times, or for which there were a sufficient number of observers to permit a study of other simultaneous changes, that a correlation of the various phenomena was possible.

In the production of a blanching of the surface of the kidney, some of the most striking of our results were obtained from an intravenous injection of *adrenaline hydrochloride*, in dosages ranging from 0·1 to 0·17 mg per kg body weight After this drug was given, the surface of the kidney was often seen to blanch very rapidly and to a remarkable degree, losing the red tinge of its normal red or perhaps reddish-brown colour and passing through stages of brown to a yellowish-white colour in cases where the effect was maximal. The size of the kidney was reduced, and the renal artery and vein showed a marked constriction. In some cases this constriction was seen to extend over the whole length of the vessels, in others it was limited to the parts adjacent to the hilum, and the more medial parts showed, on the contrary, a marked dilatation, the transition from the dilated to the constricted portions of the vessels being extremely abrupt. The colour of the blood in the renal vein darkened, and if the vein was divided there might be no bleeding from the renal side This indication that there was no circulation through the kidney was confirmed by angiographs, from which it was seen that during the period

two-thirds of the cortical zone, and presented a marked contrast to the redness of the rest of the cut surface of the kidney. In some cases there was no bleeding

from any part of the cut surface, but in others the congested medullary area bled freely, while there was no bleeding from the pallid zone of the cortex. This difference in our experiments was probably due to variations in the degree of effect produced by the adrenaline in different animals. In the former cases the effect was, no doubt, maximal and the entire renal circulation had temporarily ceased. In the latter cases the effect was less extreme, and a circulation was continuing through the medulla although the blood flow through the cortex had been arrested.

These effects of an intravenous injection of adrenaline in such a dosage are all rapid in *onset and relatively short-lived. Blanching of the kidney* may be evident within seven seconds from the time of the injection and may be maximal at twenty seconds. Recovery may be well under way within the first minute. It is noteworthy that the greatest effect is obtained from a first injection of adrenaline. Subsequent injections, made soon after the first, produce a much reduced or even negligible response.

In the earliest stage of the recovery period, a spectacular change may sometimes be seen in the renal vein. While the surface of the kidney is still *extremely pallid a streamline of bright red blood may suddenly appear in* the dark blue blood of the renal vein. This sudden appearance of arterial blood is dramatic, particularly when its flow is clearly seen to be pulsatile. If an injection of Indian ink is made at the appropriate moment, the ink may be seen leaving the kidney by the renal vein without staining the surface of the kidney.

Similar results were seen in rats after intravenous injection of adrenaline [illegible]

As an alternative to adrenaline, *ephedrine hydrochloride* was used on one occasion. After an intravenous injection of this drug in the dosage of 0·7 mg. per kg. body weight there was an almost immediate constriction of the renal artery, a blanching of the surface of the kidney, and a constriction of the renal vein in which a red streamline made its appearance.

In the course of our angiographic studies, described in Chapter II, we had observed that after an intravenous injection of *pilocarpine nitrate*, whilst the calibre of the renal artery was virtually unchanged, the renal vein showed a definite dilatation. To determine whether this dilatation of the vein was [illegible] watch- [illegible] is series of experiments; it was injected intravenously in dosages ranging [illegible] 0·4 to 0·8 mg. per kg. body weight. The surface of the kidney showed *no tendency* to blanch after administration of the drug, but the renal vein always dilated. Generally the colour of the blood in the renal vein would change to red,

but occasionally the blood was seen to darken, and presently a stream of red blood made its appearance. This stream was conspicuous not only because its colour was sharply contrasted with the dark blood adjacent to it in the vein, but also because it had a faintly pulsatile flow.

Prostigmin was used in a few other rabbits and gave results very similar to those given by pilocarpine. For example, in one animal, after an intravenous injection of this drug in the dosage of 0·1 mg. per kg. body weight, a red streamline appeared in the renal vein; this was followed by a dilatation of the renal vein and a general reddening of the venous blood. With double this dosage in another animal, a similar dilatation of the renal vein occurred and the venous blood became intensely red.

Another drug used because of its vasodilator effect was *amyl nitrite*. After inhalation of this drug marked generalised cyanosis occurred. The renal artery became dilated and its blood blue. The vein was also dilated and its blood a very dark blue.

We used *pituitrin* (posterior pituitary extract) both in rabbits and in rats. In rabbits, after an intravenous injection in a dosage ranging from 0·1 to 5·0 units per [illegible] wed either no change in calibre or else a [illegible] the kidney paled, though the degree of [illegible]s, and the paling was very transient in all cases. The blood in the renal vein was intensely red both [illegible] its to which pitui- [illegible] the blanching of [illegible] s extreme as any blanching we have seen. The onset of the pallor occurred within thirty to sixty seconds from the time of the intravenous injection, and the duration of this pallor might be up to five minutes.

Pitressin was also given to rats intravenously in dosages ranging from 0·2 to 20 pressor units per kg. body weight. The effects were very similar to those seen after the injection of pituitrin, although we noticed that the blanching of the surface of the kidney began fairly constantly within thirty seconds from the time of the injection. With a high dosage the pallor of the kidney was intense. No obvious change was detected in the calibres of the renal artery and renal vein. In these respects both pitressin and pituitrin differed from adrenaline in the effects produced, but the blanching of the surface of the kidney was as spectacular after these substances had been given to rats as it was with adrenaline in both rabbits and rats. In rats another difference from the appearance seen after an injection of adrenaline in both rabbits and rats was observed in the recovery phase, and this was particularly well seen when the pitressin had been given in high dosage subcutaneously. The surface of the kidney became mottled with irregular congested areas which alternated with the areas of pallor, whereas in the recovery period

after adrenaline the colour of the surface of the kidney changed fairly uniformly.

In a certain number of experiments on rabbits *two drugs* were administered intravenously, one after the other. When adrenaline was given after an injection of pilocarpine or of prostigmin the predominant result seen was similar to that obtained after an injection of adrenaline alone, but the appearance of the red stream in the renal vein in the first stage of the recovery phase occurred more frequently than it did when adrenaline alone was used.

The radiograph reproduced in Figure 20 shows the kidneys of a rabbit to which *adrenaline* was given (in a dosage of 0·1 mg. per kg. body weight) four minutes after an injection of *pilocarpine* (in a dosage of 0·4 mg. per kg. body weight). Thirty seconds after the adrenaline had been given an injection of contrast medium was made. Because of the interference which adrenaline was known to cause in the normal speed of the systemic circulation, owing to intense peripheral vasoconstriction, the exposure of the radiographs was purposely made at a late stage. Even the last of the serial films, however, exposed forty seconds after the injection of contrast medium, and seventy seconds after the injection of adrenaline, showed that no contrast medium had reached the renal vessels, indicating that there was virtually no circulation through the kidneys. Thirty minutes later, and ten minutes after death, a further radiograph was taken after the abdomen had been opened and the intestines displaced. In this radiograph (Figure 20) contrast medium is clearly seen in the kidneys, indicating that at some stage between the previous radiographs and the death of the animal the circulation through these organs had begun again. This radiograph is of special interest because of the distribution of the contrast medium within the kidneys. It will be seen that there is a relatively poor shadow in the cortex of both kidneys and a much denser shadow in the medulla, a fact which indicates that the circulation through the kidneys, when it was resumed, was mainly by way of the medullary pathway. Further observations of a decrease in the circulation through the cortex, with a corresponding increase in the circulation through the medulla, derived from our angiographic studies, are described in Chapter V.

When *atropine sulphate* in a dosage of 1·7 mg. per kg. body weight was given (by intravenous injection) after *pilocarpine*, the renal vein, which had become dilated and extremely red following the pilocarpine, became constricted and its contained blood darkened.

Up to this point the visual observations described have been confined to alterations in the renal circulation effected by the use of drugs. In addition, however, similar observations were made of the changes effected by some of

the experimental procedures which had previously been employed in the angiographic studies described in Chapter II.

Fig. 20 Radiograph showing a cortical ischaemia of both kidneys The heavy shadow of the medulla contrasts with the poor shadow of the cortex, indicating that the circulating contrast medium had been largely excluded from the cortex The rabbit's abdomen had been opened and the intestines displaced before the radiograph was taken For details of the experiment see text

Examination of the kidney in some of our tourniquet animals at the conclusion of the experiment had shown some degree of pallor of the surface of the kidney, combined with a redness of the blood in the renal vein. Working on our original hypothesis that nervous stimuli played an important part in the renal changes seen after crushing injuries, a hypothesis which had received some degree of support from our earlier experimental studies, we decided to substitute *stimulation of the sciatic nerve* for the lengthy procedure of the tourniquet experiment

Stimulation was applied to the central end of the divided left sciatic nerve In some cases the nerve was crushed with artery forceps, in others faradic stimulation was used. These two forms of stimuli produced comparable effects. The effects might be to some extent bilateral, but in general the left kidney, that on the stimulated side, was the one primarily or apparently solely affected The degree of the effects of our sciatic stimulation was found to vary markedly from animal to animal. In those animals in which a response was obtained, the surface of the kidney blanched, sometimes to an

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FIG. 20 Radiograph showing a cortical ischaemia of both kidneys The heavy shadow of the medulla contrasts with the poor shadow of the cortex, indicating that the circulating contrast medium had been largely excluded from the cortex The rabbit's abdomen had been opened and the intestines displaced before the radiograph was taken For details of the experiment see text

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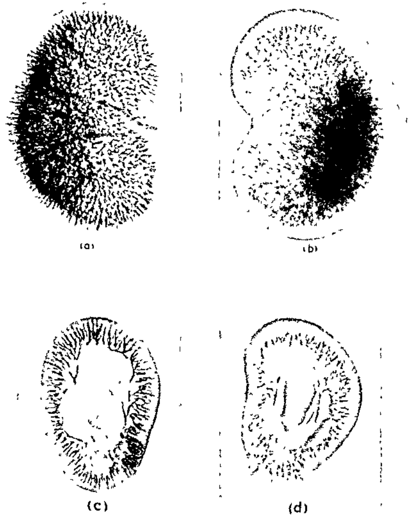
intense degree of pallor, the renal artery became constricted, and the colour of the blood in the renal vein became red. A blanching of the surface of the kidney was observed in rats as well as in rabbits after the central end of the divided sciatic nerve had been crushed with artery forceps.

In a further group of rabbits we *stimulated the distal end of the divided left splanchnic nerve.* After such stimulation the surface of the kidney tended to blanch, and red streamlines sometimes appeared in the renal vein. With this type of stimulation also the results were noticeably variable from animal to animal.

The most marked and constant effects were obtained by faradic *stimulation of the nervous plexus surrounding the renal artery.* Although we cannot definitely dissociate the effects of stimulating the nervous plexus from those of direct stimulation of the renal artery itself, we are inclined to believe that the effects seen are those obtained from the intermediation of the nerves of the renal plexus rather than from any direct muscular response. After stimulation has been applied to this plexus the renal artery becomes constricted, often to a marked degree, the kidney itself contracts and its surface blanches, the colour becoming remarkably pale. The renal vein also becomes constricted and red streamlines are frequently seen in it. If an intravascular injection of Indian ink is made at this stage, the surface of the kidney is not stained, although the ink may be seen leaving the kidney by the renal vein. The implications of this observation are even more striking when a succession of particles of ink are seen, as discrete black specks in the red blood, being carried in a pulsatile stream towards the vena cava. Such injections of Indian ink and of radio-paque substances have shown that the pallor of the surface of the kidney is due to a marked peripheral vasoconstriction, and it is therefore legitimate to attribute to the same cause the pallor of the surface of the kidneys observed in many of the experiments described in this chapter.

The diminished renal circulation and particularly the virtual absence of any cortical filling which obtain in these conditions may be seen in Figure 21.

In some of the experiments that have just been described we tried to correlate the *flow of urine* with the renal and vascular changes observed. We decided against ureteric catheterisation for recording urine flow because of the disturbance of renal function which this procedure may cause. In a few of the early experiments of the angiographic series, we had employed some of the contrast media used in excretion urography because they are eliminated from the blood stream by the kidney, and we had confirmed in rabbits that the passage of the contrast medium through the ureters was not continuous but intermittent, as if propelled by individual peristaltic waves. In the group of experiments described in this chapter, in which direct observations were made with the abdomen open, we found that individual peristaltic waves in


(a)
(b)
(c)
(d)

the ureter could be clearly seen, and accordingly we decided to use these waves as an indication of urine flow.

In those experiments in which observations of this nature were made we found that the number of peristaltic waves seen to pass along the ureter was markedly decreased when the surface of the kidney showed some degree of pallor. This suggested that there was a correlation between a diminished cortical circulation and a diminished urine flow, although we cannot exclude the possibility that the stimulus which caused the surface of the kidney to blanch also directly inhibited ureteric peristalsis.

As a result of the experiments summarised in this chapter, the suspicion which had been derived from our angiographic studies, that a short-circuiting of the blood flow might occur in the rabbit's kidney, became a conviction. Further, we learnt that when this short-circuiting occurs the blood passing through the kidney is diverted from the cortex to the medulla, and that the blood supply to the cortex may be so reduced that complete cortical ischaemia may result. We also learnt that cortical ischaemia can be produced in the rat.

As regards the use of the term 'short-circuit', the first suggestions of the existence of an alternative intrarenal pathway were derived from observations which indicated that the blood was taking a course through the kidney shorter than usual, but in the state of our knowledge at the time we had no idea as to the exact site of the 'short-circuit'. In our subsequent studies we have not as yet determined whether, when the blood is diverted from the cortex through a medullary pathway, the course taken by the blood is always shorter than that through the cortical pathway. Consequently, until this point is established we shall not in future refer to a 'short-circuit', a term which is open to misinterpretation, but shall use instead the term 'by-pass' in referring to the pathway through the medulla through which the blood is carried when it is diverted from the cortex.

In our investigations up to this stage we had studied the renal circulation from a purely functional point of view. In the next stage we concentrated our attention on a morphological study of the intrarenal vessels in an attempt to discover the anatomical channels through which the blood is directed when it is diverted from the cortex. The data provided by this study forms the subject of Chapter IV.

CHAPTER IV

Studies of the Intrarenal Vascular Pattern

THE observations that under certain conditions the blood, or substances injected into the blood stream, could pass through the kidney without traversing the peripheral and indeed the greater part of the cortex indicated that one of the next stages of the investigation must be a study of the intrarenal vascular pattern, with a view to determining the actual pathway used in these conditions. One experiment in particular (see Figure 18) had indicated that the region probably concerned was the deepest layer of the cortex and the subcortical zone. It was unlikely that there were undescribed channels between the arterial and venous sides of the circulation in this territory, for, if such channels were present, it seemed that they must be of large calibre to have been able to carry all the blood which was diverted from the cortex, and that therefore they could scarcely have been overlooked by

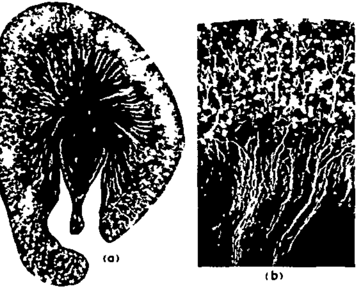
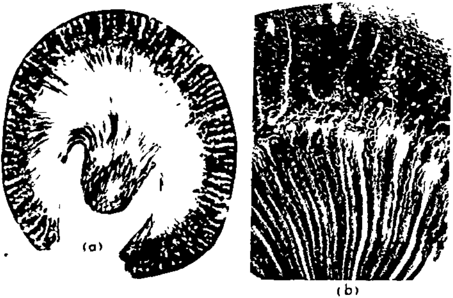


FIG 22 Photographs showing the distribution of Indian ink injected during life [illegible]

[illegible] medulla the ink is seen in vasa recta

previous workers. *Did the existing vessels, as known and described, provide a possible pathway?*



[illegible] Figure 24)

Before embarking on a detailed account of the various methods used and the results obtained in our attempts to prove that the vessels of the medulla were capable of carrying the blood diverted from the cortex, we describe first two experiments which suggested to us the general lines of our morphological studies. In these experiments, owing to the unsuitability of methylene blue (which we had used in the experiment quoted above) for a detailed study of the vessels, we used injections of Indian ink. We injected this substance during life into the renal artery of a normal rabbit, to serve as a control, and then into that of another rabbit, while applying faradic stimulation to the nervous plexus surrounding the renal artery. On radial[1] section of these two kidneys, a very striking difference was apparent in the distribution of the Indian ink. In the kidney of the normal animal (Figure 22*a*) the cortex was seen to be well and fairly evenly filled with the injection mass, while there was only a very indifferent filling of the medulla.

[1] The term 'radial' is applied to sections which are cut in planes radiating from the hilum in the short axis of the kidney

The structures responsible for this macroscopic picture were found on microscopic examination (Figure 22*b*) to consist of interlobular arteries (called by some workers 'intralobular' arteries), glomeruli and the intertubular capillary network in the cortex, and of the vasa recta and the medullary intertubular capillary plexus in the medulla. The injection had not passed through the capillary plexuses to fill the veins. In the kidney of the stimulated animal, on the other hand, the macroscopic picture (Figure 23*a*) showed a poor filling of the cortex and a very marked filling of the medulla, where the pattern consisted of close-set radial streaks. The filling was variable in different radial planes through the kidney and in some sections (Figure 24) was most conspicuous in the subcortical zone, while the apex of the medulla was relatively unfilled. Microscopically (Figure 23*b*) the well-filled vessels of the medulla were seen to be the vasa recta, whilst in the cortex some glomeruli, mainly those in the deepest zone, and a few interlobular veins were filled.

FIG 24 Another section from the stimulated kidney depicted in Figure 23, showing in this plane a particularly marked filling of the subcortical zone of the medulla (Part of this section is shown in Figure 23*b*, a less completely filled area having been selected in order to show more detail)

The results of these simple experiments suggested that:

1. In the normal animal the vessels of the cortex receive the greater part of the renal blood supply, while those of the medulla receive a noticeably smaller part.

2. In the stimulated animal the vessels of the medulla receive by far the greater part of the blood supply, while those of the cortex, with the exception of the vessels in its deepest zone, receive virtually none.

3. The vessels of the medulla, carrying in the normal animal a relatively small part and in the stimulated animal the bulk of the total intrarenal blood flow, were apparently the same in each case, namely, the vasa recta.

It will be appreciated, therefore, that our attention was immediately focussed on the vasa recta, since they appeared to form the channels through which the blood diverted from the cortex passed through the medulla.

We have been surprised to find how comparatively little interest has been taken in this part of the intrarenal vascular system Some explanation of this relative neglect of the medulla may be due to the generally prevailing concept that the important functional elements of the kidney are confined to the cortex. Moreover, although the renal vascular pattern has been studied extensively, mainly by means of injection masses introduced post mortem, our own experience, coinciding with that of Gross (1917, 1918), has shown that in the normal adult kidney an arterial injection, whilst giving a good picture of the cortical vessels, results in a relatively poor filling of the

vessels of the medulla. The difficulty of studying the vasculature of the medulla, however, does not end with the filling of these vessels, since the rarity with which sections can be cut in exactly the same plane as the vessels constitutes a further obstacle to tracing their course from beginning to end. For these and other reasons the study of the vascular arrangements in this region is not an easy one.

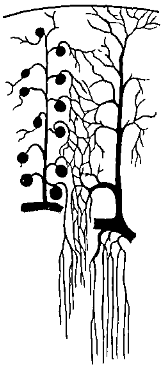


FIG 25 Incomplete, and in various respects erroneous, diagram of the smaller intrarenal vessels, such as is commonly seen in current textbooks Note in particular the way in which the vasa recta end in the medulla in space, having no apparent connection between their 'arterial' and 'venous' sides

The diagram shown in Figure 25 indicates the pattern of the smaller intrarenal vessels as generally described in the various current textbooks. It shows an 'arcuate'[1] artery giving off an interlobular artery, from which spring afferent arterioles, each leading to a glomerulus. The efferent vessels of the glomeruli of the greater part of the cortex pass to the cortical intertubular capillary network, which is drained by an interlobular vein. It will be seen, however, that the efferent vessel of the glomerulus lying nearest to the medulla breaks up into a group of more or less parallel straight vessels, the vasa recta, which pass towards the apex of the medulla. Some diagrams, including the well-known one of Cushny (1917), which is still used in several standard text-books of physiology, omit the vasa recta altogether, while many of the diagrams which do show these vessels depict them as ending in space (as in Figure 25), and as having no apparent connection with their corresponding veins. Some good descriptions and illustrations of the vasa recta have been given by various workers, including Bowman (1842), Virchow (1857), Huber (1907), Morison (1926), MacCallum (1926), Moore (1928), and Bensley (1929), and a valuable account is given in the general survey of the kidney by von Mollendorff (1930), but the complete pattern of these vessels—their size, numbers, course from beginning to end—and their relation to the renal tubules have never, as far as we know, been adequately presented. Moreover, most workers appear to have been interested mainly in the arterial side of these vessels, and detailed studies of the venous drainage of the medulla have been strangely lacking.

In this chapter we present the evidence which we have obtained that the vasa recta, together with their related vessels, constitute the medullary pathway through which

[1] In the absence of a generally acceptable term for the vessels intermediate between interlobar and interlobular, we use the traditional name 'arcuate', although we agree with Gross (1917) and Loomis (1936) that in the human kidney it is not a satisfactory designation

the blood, when it is diverted from the cortex, is carried from the renal artery to the renal vein.[1]

Materials and Methods Used

The material used in this study has been provided by the kidneys of more than one hundred and fifty rabbits, and of a smaller number of dogs, cats, rats, and guinea-pigs. In addition, the kidneys of some seventy human subjects, both normal and diseased, derived from necropsy material have been used. These last specimens were removed within six to twenty-four hours of death, complete with all perinephric tissues and with adjacent sections of the aorta and inferior vena cava. In the case of the animals, injections have been made both in vivo (under nembutal and/or ether anaesthesia) and also post mortem. In some instances the animals were not subjected to any experimental procedure other than that of the injection. In other instances the injection was made either during or after certain experimental procedures, including the administration of drugs, the infliction of trauma, and the application of electrical and other forms of stimulation.

Many types of injection mass were used (see Figures 26, 27). The most satisfactory results were obtained with the following:

1. *Indian ink.* Higgins Waterproof Black (American India Ink)[2] was the most satisfactory brand, though we found that good results could be obtained with several English proprietary Indian inks provided that they were filtered; Higgins ink could be used without filtration. The ink was diluted with from one to three parts of distilled water.

2. '*Aquadag' colloidal graphite in water.* One part suspended in three parts of distilled water.

3. *Berlin blue soluble.* This was most satisfactory in a concentration of 2 per cent made up in distilled water. We found, as Hinman, Morison, and Lee-Brown (1923) had done, that an aqueous solution of Berlin blue gave better results than the classical Berlin blue gelatine mass.

4. *Colloidal metallic bismuth.* A concentration of 10 per cent was found somewhat too viscous for easy injection and the mass was therefore diluted with an equal volume of distilled water. It still proved to be a difficult material to inject when a very fine cannula or needle was used.

5. *Colloidal metallic gold (red) 10 per cent.* This mass gave very good results, particularly in showing the finest vessels.

6 [illegible]

mate [illegible]

masse [illegible]

Figur [illegible]

vessels when sections were cut (though it suffered less from this defect when the tissue was embedded in celloidin), and a muddy appearance when sections were viewed by transmitted light.

Of the above substances the colloidal metals[3] [illegible]

ves [illegible]

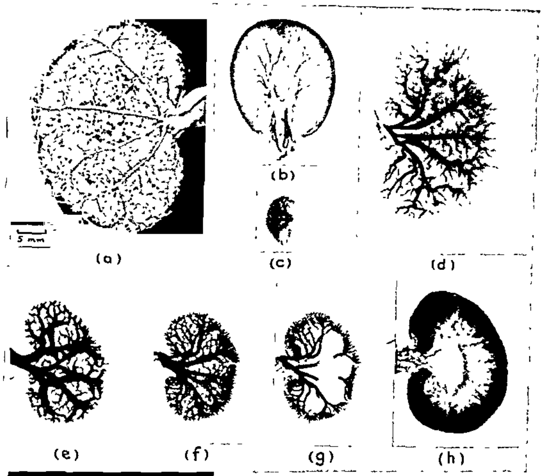


FIG. 26. Injection masses of various types (*a*) neoprene (arterial, white, and venous, blue, injec-

bismuth carbonate (venous injection), whole kidney

by the use of two non-colloidal metallic suspensions because, owing to the large size of their particles, they did not enter the profuse fine vessels and so obscure the larger vascular trunks (see Figures 26*d*, *e*, *f*, *g*) These radiopaque materials were:

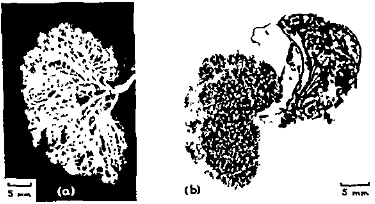


FIG 27 Neoprene casts of the vasculature of the kidney (*a*) human foetus of seven months, arterial injection (*b*) human foetus of six months, arterial (white) and venous (blue) injections. Note also in (*b*) the vasculature of the suprarenal

7 *Bismuth carbonate* A suspension of 10 per cent in tap water

8 *Red lead* (Pb_3O_4) A suspension of approximately 10 per cent in tap water

Both these substances precipitate very quickly, and the suspension must therefore be well stirred immediately prior to use.

9 *Neoprene latex* This injection mass, which was introduced for renal vascular studies by Lieb (1940) and has been used by Duff and More (1944) and by Shonyo and Mann (1944), proved to be of the utmost value The neoprene casts obtained by corrosion of the injected specimens with acid allowed us to examine the morphology of the vessels in a way that was not possible in sectioned material nor, at any rate by us, in material macerated by the meth

superior

(1923)

of various dyes[1] (see Figures 26*a*, 27)

All injection masses other than the neoprene were

was made during life or after death

Injections made during life All the injections made during life were of necessity made from the arterial side In rabbits and cats one satisfactory method frequently used was to inject, through a cannula tied into the distal abdominal aorta, pointing towards the heart, at a pressure sufficient to keep the head of the column of the injection mass just proximal to the renal arteries, the object of this was to allow the heart-beat itself to drive the mass through the renal vessels With this technique the amount injected ranged from 10 to 70 ml, and in

[1] The neoprene latex used was type 571, and the original samples, together with the aqueous colour pastes for dyeing the neoprene, were given to us by Imperial Chemical Industries, Ltd (Dyestuffs Division), through the courtesy of Mr C Falconer Flint, to whom we are also indebted for advice on certain aspects of the use of these materials

some cases the mesenteric artery was clamped or ligated prior to the injection in order to conserve the injection material A second method, used in a number of animals, was to inject a much smaller amount of material through a hypodermic needle directly into the renal artery In rats and guinea-pigs and in a series of newborn rabbits a convenient route for injection was found to be the thoracic aorta, quickly exposed by removal of part of the chest wall on the left side For these injections a hypodermic needle was used and the amount injected varied from 2 to 10 ml After the injection was completed the kidney or kidneys were quickly excised and placed in fixative

Injections made after death A cannula was tied into the renal artery and often into the renal vein also In most cases, prior to injection, the kidneys were perfused from the arterial side with tap water, or with normal or hypertonic saline, at a relatively low pressure (110 to 130 cm of water) for a varying number of hours up to twelve Occasionally a small quantity of a 10 per cent solution of sodium nitrite in warmed tap water was introduced beforehand to serve as a vasodilator The most satisfactory injections were obtained when the kidneys had become pale at an early stage in the washing After perfusion the organ was placed in the refrigerator with the cannula still in position, and left to drain for a period up to twenty-four hours The best injection results were obtained when the specimen was compressed under a moderate weight during drainage The kidney was then placed in warm water for about half an hour, and when it was thoroughly warmed the injection was made

Injections were made from the arterial side alone, from the venous side alone, and from ... the venous), superficial ... The amount of mass ... in the vessel or vessels through which the injection had been made were tied off and the organ was placed in fixative.

Injections with neoprene Considerable practice was needed before we mastered the special difficulties of this technique One of the major obstacles was the tendency of the liquid to set prematurely. We found it impracticable to use a syringe for injecting this material, owing to the fact that a film was left between piston and barrel, which set and jammed the syringe Fine cannulae, when blocked, could not be cleared, and we therefore used glass ones as these could be easily replaced Furthermore, there was always the risk that the neoprene would set in the larger blood channels before reaching the finer vessels, owing to its contact with tissue fluids

The apparatus used for making neoprene injections was very simple (Figure 28) It consisted of an oxygen cylinder fitted with a reducing valve, connected by one arm of a Y-tube to a wide-necked bottle containing neoprene, and by the other to a mercury manometer An out-flow through a T-tube ...

was introduced into the circuit between the oxygen cylinder and the manometer As a safety measure this bottle was wrapped in sacking. The cannula was attached to the ...

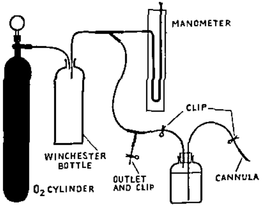


FIG 28 Diagram of apparatus used in making injections of neoprene

end of the injection, before the pressure was released, the cannulated vessel or vessels were ligated, the cannula was then removed and the kidney plunged into 10 per cent formol-saline acidified with a few ml of commercial hydrochloric acid After an hour or so in this fluid, when the neoprene in the superficial vessels had solidified, the perinephric tissues were dissected off We found in general that after this it was best to place the kidney in 10 per cent formol-saline for about a week, so as to avoid the distortion which occurs when freshly-cut organs are fixed

After this period of fixation the whole organ, or more frequently slices cut in various planes were corroded by being immersed in undiluted commercial hydrochloric acid contained in a closed vessel, and left for from twelve to twenty-four hours either on a radiator or in an oven at 56° C. The specimen was then washed by a gentle flow of water, and when the macerated renal tissue had been washed away the cast was ready for examination. The macerated casts were preserved in 1 per cent formol-tap water

For examination a cast was placed in water in a shallow glass dish and viewed through a dissecting microscope giving magnifications of from × 6 to × 200 Direct lighting provided by a high intensity lamp was used The casts were manipulated and dissected with the help of glass needles, fine forceps, and scissors

The preservation of small fragments dissected from the main cast proved to be a serious difficulty We disliked the distortion which resulted from the method of mounting advocated by Duff and More (1944), in which the cast is placed on a slide and flattened out by the pressure of a cover slip [illegible] a transparent mediu[illegible] with a thick cover sli[illegible] parent medium in wh[illegible] and Canada balsam [illegible] neoprene, rendering it transparent and thus invisible The mounting medium most generally used has been tap water (from which dissolved oxygen has been removed by previous boiling) with the addition of a trace of preservative, such as formaldehyde or thymol A thick cover slip is sealed over the cell with Reuter's dichromate gelatine Although we have found this to be a fairly good method of mounting, we are still troubled by the air bubbles which often make their appearance in the fluid in the course of a few hours or days

Histological methods used The further treatment of kidneys injected with masses other than neoprene and of the considerable number of uninjected kidneys used in this study was as follows

All the larger kidneys were cut either immediately or after a few hours' preliminary fixation The fixative used throughout was 10 per cent formol-saline and the tissues were fixed and hardened in this solution for a minimum period of two days Blocks from different parts of the kidney were cut in various planes In many instances these were embedded in paraffin or celloidin The sections cut from the paraffin blocks ranged from 5 to 8μ in thickness, and those from the celloidin blocks from 10 to 300μ Many sections from the injected material were examined unstained Other sections were stained with Ehrlich's haematoxylin and eosin, Weigert's iron haematoxylin and van Gieson's mixture, van Gieson's mixture alone, phosphotungstic acid haematoxylin, and Masson's trichrome. In addition [illegible]

through the alcohols and cleared in creosote or in a mixture of phenol-toluol-creosote and mounted in balsam. Others, both thick and thin, were stained with Weigert's iron haematoxylin and van Gieson's mixture, with van Gieson's mixture alone, and with Ehrlich's haematoxylin [1] These stains were used also for frozen sections, both thick and thin, of uninjected kidneys; some thick unstained sections of uninjected kidneys were cleared by the Spalteholz method, which was found to give a very clear picture of the red cells contained within the vessels

Sections were examined by transmitted light both through a single objective microscope and also through the binocular dissecting microscope used for viewing the neoprene casts.

use was made of stereophotomicrographs (see Figure 74) These were taken by fitting the camera attachment to each eyepiece of the dissecting microscope in turn.

* * * * *

In working out the pattern of the vascular structures of the kidney we have benefited greatly not only by the large number of kidneys studied, but also by the wide range of techniques used in our investigation.

The histological examination of thin sections of kidneys, injected or uninjected, affords but a poor and incomplete picture of the vascular pattern, but, once the pattern is understood, such an examination is of great value in showing the relations between vessels and parenchyma Thick sections of similar kidneys, unstained or very lightly stained, reveal a picture surprising to one who is familiar with thin sections only, for considerable portions of the various structures may be seen in their entirety The complex coils forming the convoluted tubules, the long straight tubules and their loops, and (in injected preparations or in those with only the red cells stained) the abundant vessels may be seen almost in relief even through a monocular microscope and with transmitted light With the stereoscopic view given by the dissecting microscope and the use of direct lighting the structures are seen to even better advantage, standing out in full relief

The partial maceration method introduced by Huber (1911), and used to such good effect by Oliver (1939, 1944-45) and his colleagues, provides a three-dimensional picture of extreme beauty and of great value for a study of the Malpighian corpuscles and the tubules, though it is less suitable for an investigation of the vascular system, owing to the poor resistance to the acid offered by the veins and their tributaries

Finally, the value of examining casts of the intrarenal vascular system made by injections of neoprene cannot be overestimated For the production of a rigid cast of the main vascular tree of the kidney, celloidin is probably the material of choice (see Figure 83) No one who has used it or seen the beautiful results obtained with this mass by workers such as Hinman,

and high tensile strength permit the manipulation of casts of even the smallest vessels without damage Incidentally, in some of our preparations injected with neoprene, we have obtained excellent casts of considerable portions of the uriniferous tubules, in addition to the blood vessels. For in some cases, when a high injection pressure has been used, the capillaries of

[1] Useful results in the case of very thick frozen sections were obtained by staining with Ehrlich's haematoxylin for a period varying from ten to sixty seconds and mounting the section without any 'blueing up' This gave sufficient staining of both nucleus and cytoplasm to show the relations of the renal parenchyma to the injected blood vessels

some of the glomeruli have been ruptured, allowing the neoprene to enter Bowman's capsule and to pass for a varying distance down the tubule As our interest up to the present has been mainly in the vascular structures of the kidney, we have not yet made any extensive study of the tubular casts thus obtained, though we have derived some useful information from this material on the relations of tubules to capillaries (see Appendix and Figure 80)

exactly the right projection, with no overlapping structures, is purely a matter of chance, and hundreds of sections may have to be examined to achieve one's object With the neoprene casts, on the other hand, which can be freely manipulated, any overlying material can be dissected away and the cast of the glomerulus can be examined from every aspect and, if necessary, may itself be dissected The advantages of this injection mass for the determination of an anastomosis are mentioned later in this chapter

Whilst we have found the neoprene injection method to be the most valuable of any one technique for the study of the intrarenal vascular pattern, we could not have attained that degree of understanding which we have reached by the use of this method alone Each technique used has played its special part in our investigation, and it is by the combined use of many methods that we have been able to provide the morphological contribution to our concept of the intrarenal circulation

Morphology of the Vessels through which the Blood is Carried when it is Diverted from the Cortex

1. RABBIT KIDNEYS

Our first experiments of the present series, described at the beginning of this chapter, had suggested that the vasa recta and their associated vessels were the channels through which the blood was carried when it was diverted from the cortex and passed through the medulla. These experiments had, however, also shown that in a normal animal an injection introduced from the arterial side resulted in a relatively poor filling of these vessels We therefore carried out some further experiments, designed on theoretical grounds, to achieve a better filling of these channels

We decided first to see if, by use of a vasodilator, we could obtain maximal filling of all the intrarenal vessels, including those of the medulla Figure 29 illustrates the result of one experiment of this group The rabbit, anaesthetised in the usual way, was given amyl nitrite by inhalation until it died, and then, after laparotomy, an injection of Indian ink was made into the renal artery When the ink was seen to be flowing freely from the renal vein this

cones, radially arranged, the apices being directed towards the papilla. While the cortex showed a considerable degree of filling, the distribution

(a) (b)

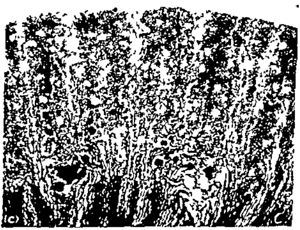


FIG 29 Sections of rabbit's kidney injected with Indian ink via the renal artery, showing remarkably good filling of medullary vessels obtained after inhalation of amyl nitrite (*a*) *coronal and (b) radial sections show that the* vasculature of the medulla has a radial arrangement The distribution of the ink in the cortex is unusual, since the interlobular arteries and the glomeruli, except for those in the deepest zone, are unfilled In (*c*), the photomicrograph, the empty glomeruli are conspicuous among the partly filled cortical intertubular capillary network This network has been filled from the venous side and the filling is attributed to reflux of ink leaving the medulla. Note some filled glomeruli in the deepest zone of the cortex (juxtamedullary) and the very good filling of the vasa recta.

of the ink in this part of the kidney was unusual The glomeruli, with the exception of those in the deepest zone of the cortex, were in general not filled and appeared as white dots against a grey-black background (Figure 29*a*, *b*). On microscopic examination (Figure 29*c*), this background was seen to consist of the cortical intertubular capillary network and some interlobular veins. [illegible] which Heggie (1946) has aptly [illegible] e most part well filled, together [illegible] a recta. It was the vasa recta which were mainly responsible for the radial pattern in the medulla which had been seen with the naked eye. We were surprised to find that few interlobular arteries showed any ink-filling except in their most proximal parts. Our original explanation of this unusual distribution of the injected mass was that the juxtamedullary glomeruli and the associated medullary channels offered an easier pathway than the vessels of the more superficial parts of the cortex, and that those interlobular veins and cortical intertubular capillaries which contained the mass had been filled by reflux from the vessels draining the medulla. Subsequent studies confirmed this view, since the location of the filled cortical intertubular capillaries showed them to belong to the venous rather than to the arterial side of the capillary bed (see Appendix and Figure 79).

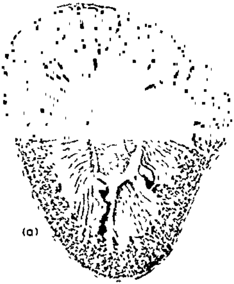
A second method used in our attempts to obtain a better filling of the medullary vessels was a mechanical one, namely, obstruction of the glomerular capillaries In the course of our angiographic studies of the effect of various forms of trauma on the calibre of vessels, we had observed an unusual feature in one or two experiments in which, over a period of many hours, we had made an exceptionally large number (eight to ten instead of the usual two to five) of thorotrast injections for angiography In the final set of angiographs we noticed a much denser shadow than usual in the cortical zone of the kidneys A further radiograph taken half an hour later, with no further injection, showed that all the contrast medium had been eliminated from the blood vessels, but that this cortical shadow remained (Figure 30*a*). Further experiments to elucidate the problem indicated that this effect was related not to any traumatic procedure, but to the large quantity of thorotrast used in the sum total of the injections and to the lapse of sufficient time for the appearance of this phenomenon. The explanation of this result is a matter for further investigation, but since radiological and microscopic examination showed that in such cases, in spite of the indications that a circulation through the kidney was maintained, the glomeruli were densely packed with thorotrast and contained little or no blood (Figure 30*b*, *c*, *d*), we decided to take advantage of this observation and see if in such conditions the medullary vessels could be filled with an injection mass. The results of one such experiment are shown in Figure 31 Intravenous injections of thorotrast were made

at intervals until the total dosage corresponded to that used in the previous animals. A radiograph taken after the last injection showed that the denser

Fig. 30 *Blockage of glomeruli of rabbit's kidneys resulting from an exceptionally large number of injections of thorotrast (For further details see text)* Note the dense cortical shadow in the radiographs (*a*) of kidneys in situ, and (*b*) and (*c*) of thick sections of these kidneys. (*d*) photomicrograph of glomerulus in periphery of cortex of one of these kidneys, showing thorotrast blocking glomerular capillaries Compare with (*e*), a glomerulus from the kidney of a normal rabbit

cortical shadow was beginning to appear, and the rabbit was put aside for a further period of time to permit the elimination of the greater part of the thorotrast which still remained in the circulating blood. The abdomen was then opened and an injection of Indian ink was made into the renal artery In Figure 31 we reproduce a radiomicrograph (Barclay, Daniel, Powell, and Prichard, 1946) of a radial section of this kidney and also a photograph of the same section, which show the distribution of the thorotrast and of the ink respectively.

The *radiomicrograph* (Figure 31*a*) shows the thorotrast filling the glomeruli, and a small quantity of the contrast medium is also seen in the vasa recta. The *photograph* (Figure 31*b*) shows the good medullary filling of ink for which we had hoped, but it shows also a considerable cortical filling. This result surprised us, but when we came to examine the sections of this kidney microscopically (Figure 31*c*) we found that there was a differential distribution



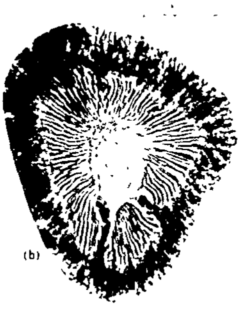


FIG 31 Good filling of medullary vessels obtained with arterial injection of Indian ink after blockage of glomeruli in peripheral cortex with thorotrast (see text and also Figure 30) (a) radiomicrograph of section of kidney showing [illegible]

kidney, showing full width of cortex and subcortical zone of medulla Note the thorotrast in peripheral glomeruli (seen as grey, rounded spots) The ink (black) is seen filling deep (juxtamedullary) glomeruli, vasa recta, and some venous vessels of the cortex

of thorotrast and ink among the glomeruli Whereas the majority of the glomeruli lying in the more superficial part of the cortex were filled with thorotrast, many of those in the juxtamedullary region were filled with ink, and the efferent vessels of these latter glomeruli were seen to be carrying the mass to the well filled vasa recta of the medulla. We were unable to satisfy ourselves of the presence of anastomoses between the interlobular arteries and the corresponding veins, and it seemed to us that much of the diffuse filling of ink in the cortex was probably the result of reflux, as in the experiment with amyl nitrite described above, since the ink was seen to be mainly in interlobular veins and their associated capillaries

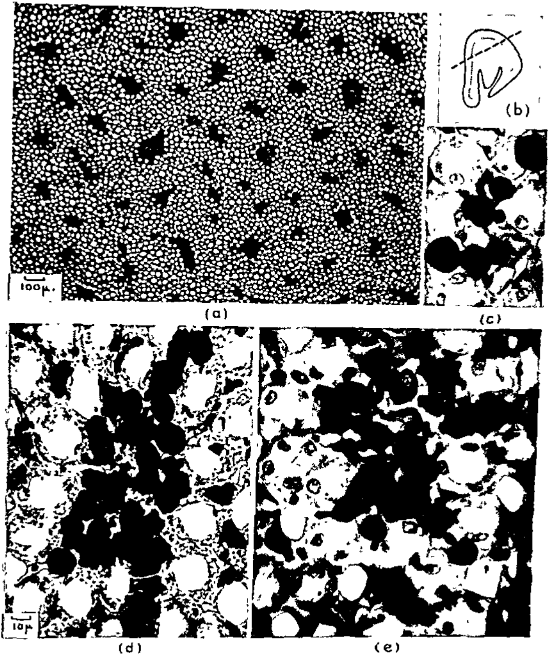


FIG 32 Tangential sections of kidney illustrated in Figure 31 Plane of section is indicated in (*b*). (*a*) low power view, showing arrangement of vasa recta in compact groups among the tubules (*c*), (*d*), and (*e*) higher power views (all at same magnification) showing the large calibre of many of these vessels, the majority are filled with Indian ink, but some are filled with blood or thorotrast (see, for example, *e*)

Tangential sections (Figure 32) cut through the medulla of this kidney showed that the vasa recta were grouped in close-set bundles, the bundles themselves being apparently arranged in a definite pattern amongst the tubules (see also Figure 40). It was seen that in each bundle of vasa recta only a certain proportion of vessels were filled with ink; the remainder were filled with red blood cells and with thorotrast. Radial sections of this kidney had shown that the vasa recta were vessels of large calibre, but in the tangential sections their large size was seen even more clearly and it was obvious that these vessels were capable of carrying a large volume of blood.

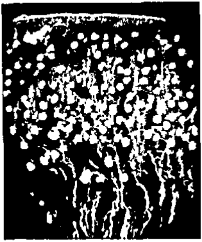


FIG 33 Low power photomicrograph showing the larger size of the glomeruli which are situated in the deeper parts of the cortex of the rabbit's kidney The injection mass used was colloidal silver iodide, introduced from the arterial side, the photomicrograph was taken with direct lighting

The juxtamedullary glomeruli and their efferent vessels

Our next object was to try to trace the course of these large medullary vessels to see if we could follow any of them from their origin on the arterial side to their termination in one of the collecting veins. Examination of the cortex of the rabbit's kidney reveals at once that the juxtamedullary glomeruli, that is to say, the glomeruli situated in the deepest zone of the cortex, are somewhat larger than the glomeruli which lie nearer to the periphery (Figure 33) This difference in size concerns not only the glomerulus itself but also its efferent vessel and the vascular bed into which the efferent vessel empties (see Figures 34, 35, and also diagram in Figure 54*b*). Whereas the efferent vessel of the glomerulus situated in the more superficial parts of the cortex is very much smaller in calibre than the afferent arteriole of the same glomerulus, the efferent vessel of the juxtamedullary glomerulus is often nearly as large as the afferent arteriole of its own glomerulus. Similarly, the efferent vessel of the glomerulus situated in the more superficial parts of the cortex empties into capillaries of small calibre forming part of the cortical intertubular capillary network, while the efferent vessel of the juxtamedullary glomerulus proceeds towards the medulla for some distance as a single large trunk before dividing into a group of parallel vessels, the vasa recta, the calibre of each of which is little smaller than that of its parent trunk (Figures 36, 37, and also diagram in Figure 54*b*).

We consider the difference between the two types of glomeruli to be of

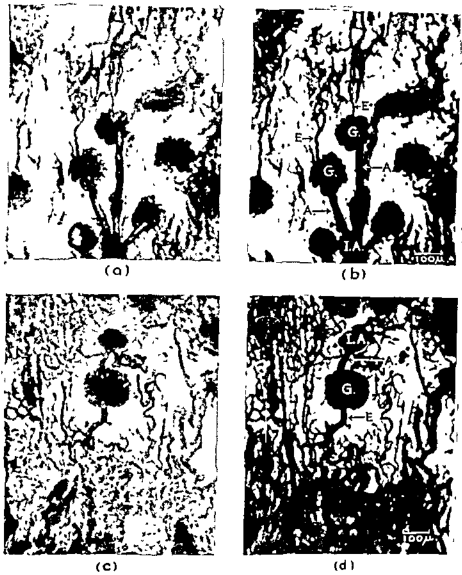


FIG 34
side with Ir

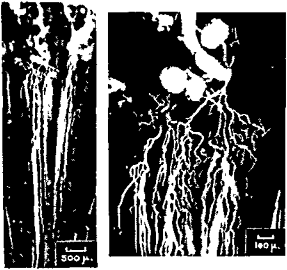
essels of the cortical glomeruli in (a) and (b), and the large calibre of the efferent vessel of the juxtamedullary glomerulus in (c) and (d) Note also the difference in size between cortical and juxtamedullary glomeruli

such fundamental importance that we distinguish between them throughout by using the prefixes cortical and juxtamedullary.[1] Our definition is based

Fig 35 Neoprene casts showing difference between (*a*) cortical and (*b*) juxtamedullary glomeruli in the rabbit's kidney Observe the small calibre of the efferent vessels of cortical glomeruli and the much larger calibre of the efferent vessels of juxtamedullary glomeruli (Scale for upper photomicrographs in each case as for lower ones)

on the intrinsic characteristics of the efferent glomerular vessel and of the vascular bed into which it empties *The term* **cortical glomerulus** *is used to denote a glomerulus whose efferent vessel is of small calibre and which breaks up to*

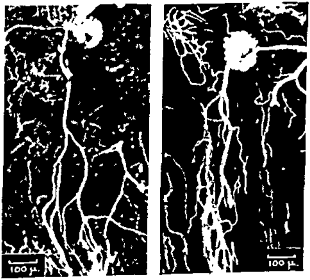
[1] Morison (1926) classifies glomeruli under four head [illegible]



(a) (b)

FIG 36 Photomicrographs of section of rabbit's kidney injected from the arterial side with Berlin blue To show the efferent vessels of juxtamedullary glomeruli dividing into vasa recta which pass in bundles deep into the medulla (*a*)

(*b*), a detail of (*a*), shows that the individual vasa recta are little smaller in calibre than their parent trunk, the efferent glomerular vessel



(a) (b)

FIG 37 Details (*a*) of Figure 22*a*, and (*b*) of Figure 31*c*, to show efferent vessels of juxtamedullary glomeruli dividing into vasa recta Note in (*b*) capillary offshoots from efferent glomerular vessel and from proximal parts of vasa recta

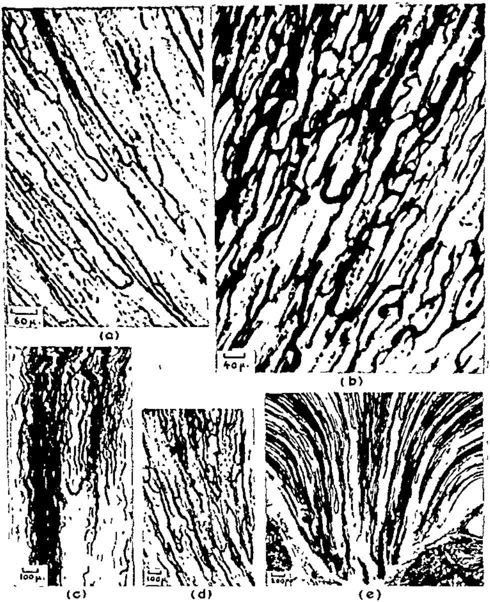


FIG. 48. Photomicrographs of sections of injected rabbits' kidneys showing [illegible] the rest are from the kidneys of adults.)

form part of the cortical intertubular capillary network. We use the term **juxtamedullary glomerulus** *to denote a glomerulus whose efferent vessel is of large calibre and which passes into the medulla to divide into vasa recta.* The juxtamedullary glomeruli are situated in the deepest zone of the cortex and are supplied by afferent arterioles arising in most instances from the proximal portions of the interlobular arteries, but occasionally also directly from an 'arcuate' artery. The cortical glomeruli lie in all zones of the cortex peripheral to the zone in which the juxtamedullary glomeruli are found, and some are also seen in this deepest zone.

The vasa recta and their course

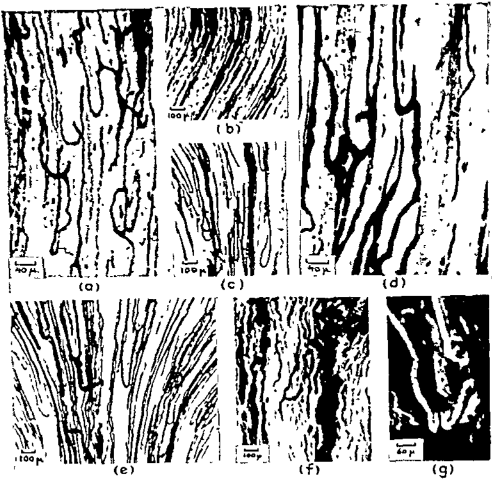
The most striking features of the vasa recta are their large calibre, their straightness, and the fact that they are grouped together in compact bundles. In these bundles individual vasa recta are frequently contiguous, as may be seen in Figures 40, 41, 43*b*, and 49*b*. Further, their walls are composed of only a single layer of pavement epithelium and are thus identical in structure with the walls of capillaries. We are not familiar with such a vascular pattern elsewhere in the body, and this curious arrangement, by which a thin-walled vessel may be almost completely surrounded by other vessels of the same type lying adjacent to it, seems to be a characteristic belonging exclusively to these vessels of the renal medulla.

In tracing the course of these bundles of vessels we experienced some difficulty Frequently the more distal parts were not filled with the injection mass and equally often the plane of section did not correspond with the plane of the vessels, so that they were cut obliquely across at various levels (see, for example, Figure 44*d*). When we were able, however, to follow their course we found, particularly in coronal[1] sections, that at various levels in the medulla individual vessels of the bundles of vasa recta turned back hairpin-wise towards the cortex (Figures 38, 39). In many instances we saw a Y-shaped formation, one limb of the vessel bending sharply back towards the cortex, but also having a continuation, often only partially filled, passing towards the medullary papilla. These loops[2] and their various modifications were seen in preparations injected from both the arterial and the venous sides. Thus, whereas near the cortex the bundle is composed of a large number of vessels, this number is steadily reduced as a result of the turning back of individual vessels as the bundle passes towards the medullary papilla.

It is extremely instructive to follow the course of these vasa recta down through the medulla in a series of tangential sections. We have done so with both injected and uninjected kidneys, and in the latter case have revealed

[1] We use the term 'coronal' section in referring to a section cut in the long axis of the kidney and passing through the hilum

[2] We use the term 'loop' to describe the sharp turn back towards the cortex of individual vasa recta, because the appearance so closely resembles that of the segment *of the tubule which is termed the* 'loop' of Henle



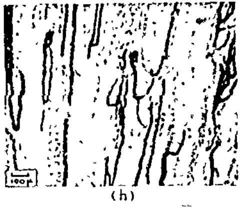


Fig 39 Further examples of loops of vasa recta at various levels in the medulla of injected rabbits' kidneys Note Y-shaped formations in (*b*), (*d*), (*e*), (*f*), *and* (*h*) *The kidneys illustrated* in (*f*) and (*g*) were injected from both arterial and venous sides (arterial injection, colloidal silver iodide, venous injection, Indian ink). (*g*) shows loops in vasa recta at apex of medullary papilla

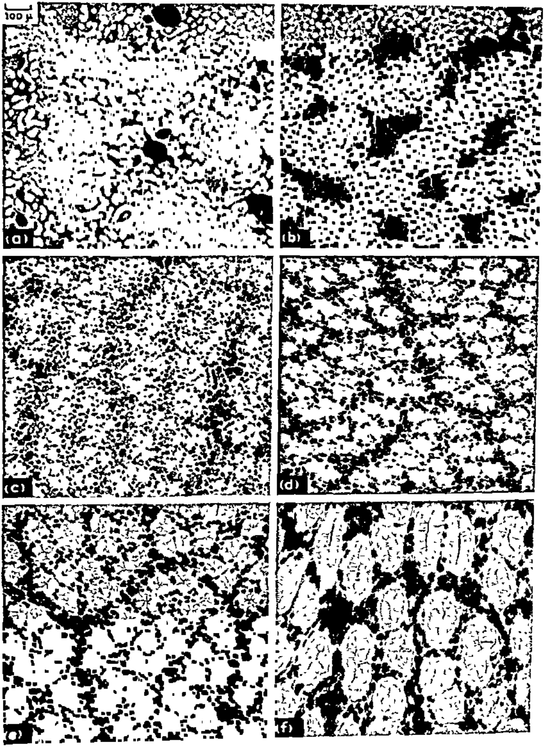


Fig 40

a very striking picture by staining the red cells alone by means of the phloxin-tartrazine method. Figures 40 and 41 show a series of such sections through the medulla and the honeycomb appearance which they present. It will be seen that in the subcortical zone (Figure 40*a*) each bundle of vasa recta contains a great number of individual vessels, but that by the time the apex of the papilla is reached (Figure 40*f*) the number of vessels in each bundle is markedly less, though the calibre of the individual vessels is relatively unchanged. It is this decrease in the number of vessels making up the bundle that gives the conical appearance of the filled medullary vessels which is seen in radial and coronal sections (Figures 23, 24, 29, 31). Injected preparations show that the smaller vasa recta constitute the 'arterial' components and the larger the 'venous' components of the system. Further, examination of this series of tangential sections shows that the bundles of vasa recta are grouped amongst the tubules in a pattern which must have a definite significance, but which we have not yet studied in detail. Some observations on the relations of the vasa recta to the tubules will be made later in this chapter. In sections stained by one of the connective tissue stains (Weigert's iron haematoxylin and van Gieson, or Masson's trichrome method), it is seen that the bundles of vasa recta are supported by a connective tissue stroma, and it seems possible that this connective tissue may to some extent account for their having escaped a closer study by users of the maceration method Moreover, as Oliver (1939) pointed out and as we have observed for ourselves, the veins withstand the action of the strong acid less well than the other structures, a fact which would explain the comparative neglect of the study of the venous side of the vasa recta by users of this method

Preparations injected from the venous side show that the 'venous limbs' of the vasa recta pass peripherally to end in a collecting vein in one of several ways Some venous limbs end directly in an 'arcuate' vein; others join an interlobular vein either directly, or else very commonly indirectly, through a short stout tributary which enters the interlobular vein near its base at right

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FIG 40 Tangential sections showing the vascular pattern at various levels of the rabbit's kidney (Sections stained by the phloxin-tartrazine method Photomicrographs at same magnification throughout)

(*a*) Cortex In the centre of the field an interlobular artery is seen with its corresponding vein (larger) adjacent to it Around this central core there is a 'venous' capillary plexus enmeshing convoluted tubules, peripheral to this plexus, groups of smaller, 'arterial' capillaries are seen outlining the straight portions of the tubules forming the medullary rays In the medulla (*b* to *f*) the pattern is very different owing to the absence of glomeruli and convoluted tubules

(*b*) to (*f*) Med [illegible]

angles. Since many venous limbs of the vasa recta end in one of these tributary veins, this group of vessels has a very characteristic appearance, resembling a comb, the teeth of which are formed by the venous terminations of the vasa recta. As the interlobular veins are peripheral to the large 'arcuate' veins, and as many vasa recta drain into their short stout tributaries, the 'arcuate' veins are frequently almost obscured by a cascade of vessels which sweep around them on the way to their venous terminations.

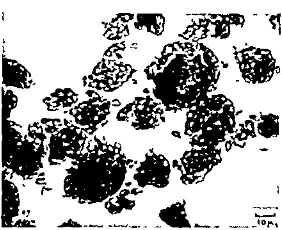

FIG 41 Higher powered view of a group of vasa recta seen in a tangential section of the medulla of a rabbit's kidney similar to those illustrated in Figure 40 (Phloxin-tartrazine stain)

It will thus be seen that the vasa recta provide a pathway of considerable capacity, which makes it possible for the blood to pass from the 'arcuate' and proximal parts of the interlobular arteries, via the juxtamedullary glomeruli, to the corresponding veins without traversing a capillary *network*.

The great vascularity of the subcortical zone of the medulla

As has already been indicated, the vasa recta show loops of a relatively simple character at virtually all levels in the medulla, but in the subcortical zone the vascular pattern is more complex than elsewhere (Figure 38*b*). We studied this zone with particular interest because it corresponded to the area so strikingly stained in all experiments in which the peripheral cortex had been excluded from the circulation as a result of various forms of stimulation (see, for example, Figure 18*d*). As a result of our studies we were able to establish certain definite facts:

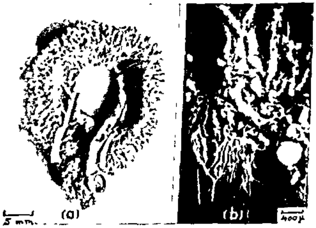

FIG 42 Part of a neoprene cast of the vessels of a rabbit's kidney Arteries, white, veins, grey (*a*) shows the great vascularity, largely venous, of the subcortical zone (*b*) detail, showing difference in size and pattern of vasa recta (below) and cortical intertubular capillaries (above)

1. The efferent vessels of the juxtamedullary glomeruli divide into vasa recta in this zone (Figures 36, 37). Groups

of vasa recta, derived from the efferent vessels of more than one juxtamedullary glomerulus, run closely together and form the 'arterial' components of a vascular bundle which, together with the 'venous' vasa recta, make up one of the vascular cones seen in several of our figures. In the normal young adult rabbit we have seen no 'arteriae rectae verae' (see p. 85), our findings in this respect agreeing with those of MacCallum (1926, 1939).

2 From the efferent vessels of the juxtamedullary glomeruli and from the most proximal parts of the vasa recta there arise vessels of capillary size which lead to a capillary network surrounding some of the tubules in this zone (see Figures 34c, 37b)

3. Many of the vasa recta turn back towards the cortex in this zone (see Figure 38 *b*, *c*)

4. There is a vast vascular bed here in which the venous elements are very prominent (Figure 42)

5 Many of the vessels in this zone differ from the characteristic vasa recta deeper in the medulla in that they run a somewhat serpentine course (Figure 43*a*). The straightness or tortuosity of the vessels in the zone is paralleled by the straightness

(Figure 43*b*) is paralleled by the straightness of the adjacent portions of the medullary tubules

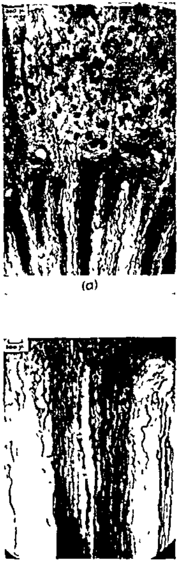

FIG 43 Sections of injected rabbits' kidneys, showing bundles of vasa recta Note the compact grouping of these vessels and, in (*a*), the slight tortuosity in the subcortical zone In (*b*), the large calibre of individual vasa recta is clearly seen

Morphological evidence that the juxtamedullary glomeruli and the vasa recta form a by-pass through the medulla

As will have been appreciated, our approach to the study of the intrarenal vascular pattern of the rabbit was different from that of most other workers because our physiological findings had shown that anatomical pathways must exist to allow of a diversion through the medulla of some or all of the cortical blood flow

In our morphological studies we found that there was a conspicuous difference between the efferent vessels of the glomeruli situated in the more superficial parts of the cortex (cortical glomeruli), and those of the glomeruli lying in its deepest zone (juxtamedullary glomeruli). *The efferent vessel of the cortical glomerulus is of small calibre; that of the juxtamedullary glomerulus is of large calibre.* It is obvious that the number of cortical glomeruli greatly exceeds that of the juxtamedullary glomeruli, though we have made no quantitative studies on this point.[1] But this disparity in numbers does not vitiate our physiological observations that under certain conditions the intrarenal blood flow can by-pass the more superficial parts of the cortex and circulate only through its deepest zone and through the medullary channels. For our studies have shown that in many cases, when this diversion of the blood flow from the cortex through the medullary by-pass occurs, the calibre of the renal artery is reduced, and this fact, together with evidence of intrarenal vasoconstriction (see Figure 21*d*) and in the absence of any evidence to the contrary, suggests that in these cases the amount of blood flowing through the kidney is diminished. In some instances, however, the diversion is not related to vasoconstriction, for example, that seen in the amyl nitrite experiment (see Figure 29) In these cases the dilatation of the juxtamedullary glomeruli and their associated vessels obviously enables them to carry an increased blood flow; indeed, it appears that these vessels, as a result of their active dilatation, afford a pathway of reduced resistance, with the result that a large volume of blood which would normally traverse the cortex now circulates through the medullary by-pass

We found also that the vascular beds supplied by the efferent vessels of these two types of glomeruli were of a totally different form and capacity. *The efferent vessel of the cortical glomerulus empties into a network of cortical capillaries of small calibre; that of the juxtamedullary glomerulus empties directly into straight medullary vessels of large calibre, the vasa recta,* giving in addition a few small offshoots to a capillary network.

The contrast in size between the efferent vessels of the cortical and juxtamedullary glomeruli, and in size and pattern between the respective vascular beds into which they empty, is in itself impressive, but when viewed in the light of physiological evidence that the greater part or all of the intrarenal blood flow can be diverted from the vessels associated with the cortical glomeruli to those associated with the juxtamedullary glomeruli, the contrast acquires a special significance.

[1] Heggie (1947) *finds that in the rabbit the juxtamedullary glomeruli make up 15 per cent of the total number* of glomeruli in each kidney, and has calculated, from measurement of their capillary volume, that they can accommodate the whole normal glomerular capillary blood volume.

Finally, we saw not only that an intertubular capillary network is supplied from the efferent vessels of the juxtamedullary glomeruli and from the proximal parts of the vasa recta, but also that *many of the vasa recta themselves turn back towards the periphery in the subcortical zone.*

These various morphological findings, taken in conjunction, provided the anatomical counterpart to our previous physiological observations. In the present stage of our studies we cannot say what proportion of the blood diverted from the cortex to the medullary channels passes through the loops of the vasa recta, and what proportion traverses the intertubular capillary network of the medulla which is supplied by these vessels, but we have no doubt whatever that the system of vessels in the zone just described is capable of carrying all blood which is diverted from the cortex, whether the amount be small or large

II HUMAN KIDNEYS

While the human kidney differs from that of the rabbit in being multilobular, we have found no fundamental difference between the minute vascular pattern of the individual lobules of the adult human kidney and that of the single lobule of the rabbit's kidney.

Bowman (1842) and Pai (1935) found that in human kidneys the juxtamedullary glomeruli were larger than the cortical glomeruli, as we have found to be the case in the rabbit. We ourselves, however, have not observed that a difference in size between these two types of glomeruli is a constant feature in the normal adult human kidney, though it is evident in the kidneys of the human foetus and of the newborn In the light of our concept of the significance of the medullary vascular pathways it is of particular interest that in foetal and neonatal life the cortex makes up a much smaller proportion of the total renal substance than it does in adult life, with a corresponding predominance of the medulla. Histological examination of the kidneys of young human foetuses reveals, moreover, that the juxtamedullary glomeruli are more completely formed than the cortical glomeruli, which at the earliest stages of development do not even resemble glomeruli. In addition, the juxtamedullary glomeruli and the vessels of the relatively large medulla, which we consider to constitute the primitive vasa recta system, are seen to be packed with red cells, in contrast with the relatively sparse distribution of these cells throughout the rest of the poorly developed cortex These observations suggest that the juxtamedullary glomeruli and their associated vessels have a particular significance in early life.

In the adult human kidney, although we have not distinguished ar

FIG 44 Sections of human kidney injected with Indian ink, showing difference between cortical (*a*) and (*b*) and juxtamedullary (*d*) glomeruli Photomicrographs (*a*), (*b*), and (*d*) taken with direct lighting, (*c*) and (*e*) with transmitted light to serve as keys to (*b*) and (*d*), same magnification throughout

A, afferent arteriole of glomerulus *E*, efferent vessel of glomerulus *G*, glomerulus *I A*, interlobular artery *V R*, vasa recta, cut obliquely across Note in (*a*) and (*b*) the small size of the efferent vessels of the cortical

Figure 47c)

constant difference in size between the cortical and juxtamedullary glomeruli themselves, we have been greatly impressed by the difference in the calibre

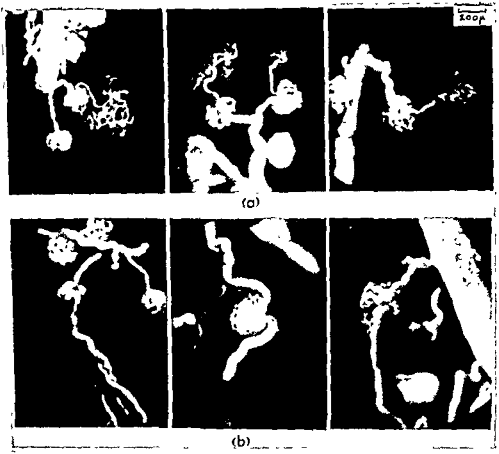

FIG 45 Neoprene casts of (*a*) cortical and (*b*) juxtamedullary glomeruli of human kidneys Note the contrast between the small efferent vessels of the cortical glomeruli (*a*) and the large efferent vessels of the juxtamedullary glomeruli (*b*) Photomicrographs at same magnification throughout The left hand pair are casts of glomeruli from the kidney of a boy aged twelve, the other casts are from adult kidneys

of the efferent vessels of these two types of glomeruli This difference is even more marked in the human kidney than it is in that of the rabbit. In the case of the cortical glomerulus the efferent and afferent vessels show the same relative proportions as they do in the rabbit, but in the case of the juxtamedullary glomerulus the efferent vessel, in the human kidney, is not only much larger than the efferent vessel of the cortical glomerulus, as it is in

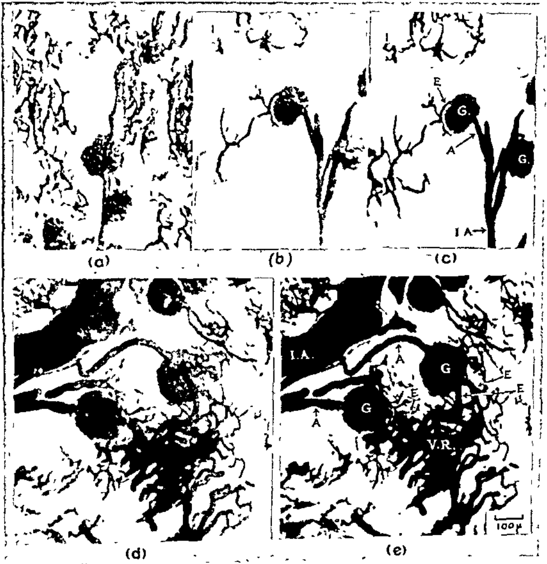

Figure 47(c)

constant difference in size between the cortical and juxtamedullary glomeruli themselves, we have been greatly impressed by the difference in the calibre

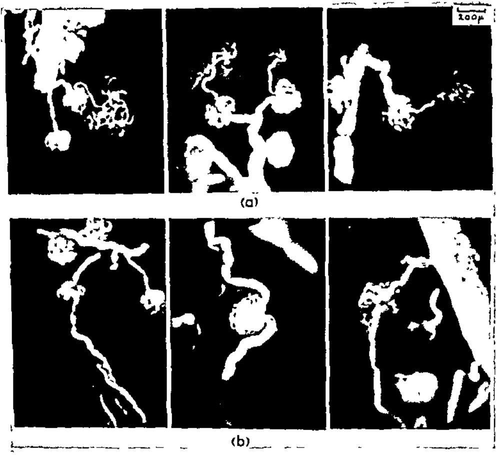

FIG 45 Neoprene casts of (*a*) cortical and (*b*) juxtamedullary glomeruli of human kidneys Note the contrast between the small efferent vessels of the cortical glomeruli (*a*) and the large efferent vessels of the juxtamedullary glomeruli (*b*) Photomicrographs at same magnification throughout The left hand pair are casts of glomeruli from the kidney of a boy aged twelve, the other casts are from adult kidneys

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the rabbit, but it is also often noticeably larger than the afferent vessel of its own glomerulus The very small size of the efferent vessel of the cortical

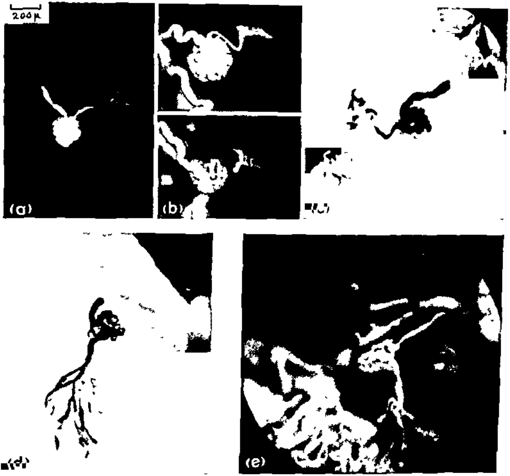

FIG 46 Neoprene casts from human kidneys to show difference in characteristics of cortical and juxtamedullary glomeruli (*a*), (*b*), and (*c*) cortical glomeruli (*b*) shows two views of the same glomerulus, note in the lower view the efferent vessel emerging from the centre of the tuft, a characteristic feature seen also in the right hand pair of glomeruli in Figure 45 (*d*) and (*e*) juxtamedullary glomeruli The large size of the efferent vessels of these glomeruli is well seen (Same magnification throughout)

glomerulus, and the strikingly large size of the efferent vessel of the juxtamedullary glomerulus in the human kidney are clearly seen in Figures 44 to 46, and are also shown diagrammatically in Figure 54*b*. In some instances the juxtamedullary glomerulus has two efferent vessels, the calibre of each of which is equivalent to that of the afferent arteriole of the glomerulus (Figure 47*c*). Occasionally one afferent arteriole supplies two juxtamedullary

glomeruli, each of which has an independent efferent vessel of characteristic size and form (Figure 47*d*).

FIG. 47 Further examples showing the difference in calibre between the efferent vessels of cortical and juxtamedullary glomeruli in the human kidney (*a*) and (*b*) cortical glomeruli. (*c*) and (*d*) juxtamedullary glomeruli Note in both (*a*) and (*c*) that the glomeruli have two efferent vessels (see also Figure 44*d*) Note also the marked difference in the size of the respective vascular beds into which the efferent vessels of these two glomeruli empty In (*d*) a single afferent arteriole supplies two glomeruli, each of which has its own efferent vessel (Photomicrographs of neoprene casts, all at the same magnification)

The efferent vessels of the juxtamedullary glomeruli pass into the medulla, breaking up to form the 'arterial' components of the bundles of vasa recta in a manner essentially similar to that seen in the rabbit (see Figure 48, and

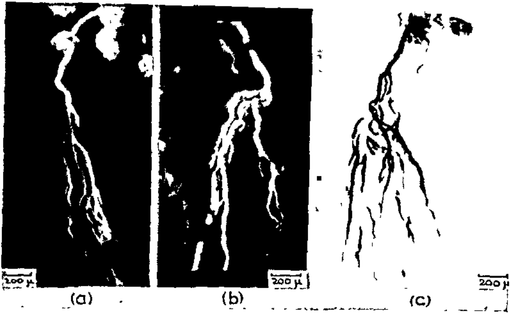

Fig 48. Casts from neoprene preparations of human kidneys, showing efferent vessels of juxtamedullary glomeruli dividing into vasa recta Note the great size and straightness of these latter vessels

Fig 49 (*a*) Section of human kidney injected with Indian ink from the arterial side, showing vasa recta and capillaries in the subcortical zone of the medulla Note the close-set bundle of vasa recta and the great calibre of these vessels as compared with the adjacent intertubular capillaries Compare this section with that shown in (*b*), which illustrates a similar bundle in the subcortical zone of a rabbit's kidney (Both photomicrographs at same magnification)

compare with Figures 36*b* and 37). A medullary capillary network is partly supplied from the efferent glomerular vessels and also from the proximal

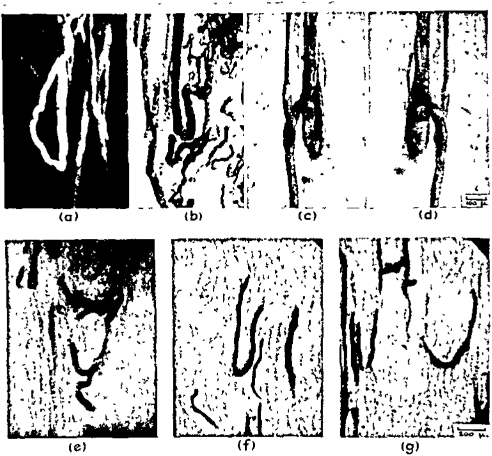

FIG 50 Loops of vasa recta in human kidneys, injected with various masses Note the complex forms of loops in (*b*) to (*d*) and the Y-shaped formations seen in (*e*) and (*g*) (*a*, *e*, and *f* same magnification as *g*, *b* and *c* same magnification as *d*)

parts of the vasa recta, but it is not always filled by injection masses. The disproportion in calibre between the vasa recta and these capillaries is well seen in Figure 49*a*, where a bundle of vasa recta is seen adjacent to this capillary network It is interesting to compare this bundle of vasa recta in a normal human kidney with a similar bundle in a normal rabbit's kidney (Figure 49*b*)

Injected preparations show individual vasa recta turning back towards the cortex, forming loops of hairpin-like appearance similar to those seen in the

vasa recta of the rabbit, and the Y-formations observed in the rabbit's medulla are found also in human preparations (Figure 50). The dense vascularity in the subcortical zone, particularly of the venous system, is as striking as it is in the rabbit (Figure 51). The continuity of the pathway from 'arterial' to 'venous' vasa recta through the loops just described has been demonstrated in kidneys which have been injected with neoprene of two different colours via the renal artery and the renal vein respectively (Figure 52). In cleared mounted sections, stained or unstained, it is extremely difficult to be certain that two masses injected from the arterial and venous sides respectively have actually joined, even when the masses are of different colours and when the preparation is examined under a binocular stereoscopic microscope, since one vessel passing closely beneath another may perfectly simulate a junction. The cast obtained from an injection of neoprene, however, provides a preparation which can be manipulated with fine forceps and glass needles beneath the dissecting microscope, and the existence of a junction can be definitely proved or disproved, for, when two columns of differently coloured neoprene actually meet each other[1] in their liquid state, they are found when set to be firmly fused and to withstand traction with a tensile strength equal to that of a continuous column of the same size

FIG 51 Photomicrograph of neoprene cast, showing dense vascularity of subcortical zone of medulla of human kidney White neoprene had been injected from the arterial side and blue neoprene from the venous Note the great number of vasa recta, in one of which a loop may be seen (at the bottom of the field slightly to left of centre)

As in the case of the rabbit, we have followed the course of the vasa recta through the medulla in a series of tangential sections, although the cutting of blocks in the appropriate plane through a multilobular kidney such as the human presents considerable difficulties. These tangential sections show that there is no fundamental difference in the arrangement of the vasa recta from that seen in the rabbit (see Figure 53, and compare with Figure 40*b*). As, moreover, many of the vasa recta turn back towards the cortex as they do in the rabbit, there is a similar diminution in the number of individual vessels of each bundle as the latter passes towards the medullary papilla. The

re-expansion

supporting stroma of the bundles of vasa recta is, however, somewhat heavier than it is in the rabbit

Relations of cortical and juxtamedullary vasculo-nephric units[1]

The relations of the medullary segments of the tubules (the loops of Henle) to the vasa recta system are obviously of profound importance. Whilst we are not yet in a position to give a detailed account of the exact relations, some observations can be made which are based partly on our own findings and partly on the accounts of other workers, especially the detailed studies of the tubules by Peter (1909, 1927) and Huber (1911, 1935).

FIG 52 Cast of vasa recta in subcortical zone of medulla of human kidney White neoprene had been injected via the renal artery and blue neoprene via the renal vein Note the two loops, one all white, and the other (to the right and slightly above) partly white and partly blue, the result of fusion of the two injection masses The arterial injection has passed below the level of the loop and thus a Y-shaped formation has been produced (see Figure 50 *e* and *g*)

As a result of an examination of the cut surface of fresh kidneys, Peter (1909) described in the medulla an outer and an inner zone He subdivided the outer zone into two bands, an outer and an inner one. Peter's 'outer band' corresponds with the zone which we describe as the subcortical zone in referring to the vascular pattern According to Peter the parts of the tubules lying in the outer zone are those parts which form the thick segments of the loops of Henle, the thin segments of some of these loops, and collecting tubules. The inner zone contains only thin segments of the loops of Henle and collecting tubules.

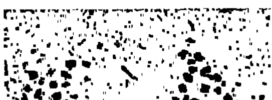

FIG 53 Tangential section of subcortical zone of medulla of human kidney, showing large calibre of vasa recta and their arrangement in compact groups (compare with Figure 40*b*) Note the presence of thin segments of loops of Henle amongst the vasa recta (Phloxin-tartrazine - - -

We were struck by the arrangement pictured by Peter (1909) in his diagrams of the renal tubules, of one of which we give a simplified version in Figure 54*a*. It will be seen that two types of nephron are shown, one with a long and the other with a short loop of Henle. The tubule with the long loop of

[1] The term vasculo-nephric unit
with a single glomerulus These
efferent vessels, and on the other t

(juxtamedullary) situated in the deepest part of the cortex, and that with the short loop arises from a glomerulus (cortical) lying in the superficial

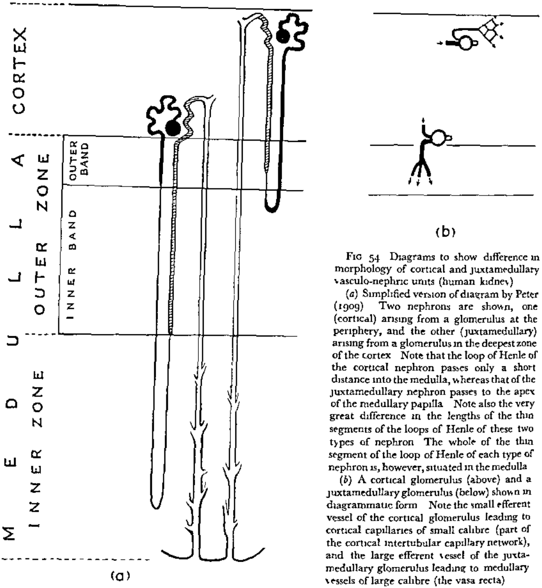

FIG 54 Diagrams to show difference in morphology of cortical and juxtamedullary vasculo-nephric units (human kidney)

(*a*) Simplified version of diagram by Peter (1909) Two nephrons are shown, one (cortical) arising from a glomerulus at the periphery, and the other (juxtamedullary) arising from a glomerulus in the deepest zone of the cortex Note that the loop of Henle of the cortical nephron passes only a short distance into the medulla, whereas that of the juxtamedullary nephron passes to the apex of the medullary papilla Note also the very great difference in the lengths of the thin segments of the loops of Henle of these two types of nephron The whole of the thin segment of the loop of Henle of each type of nephron is, however, situated in the medulla

(*b*) A cortical glomerulus (above) and a juxtamedullary glomerulus (below) shown in diagrammatic form Note the small efferent vessel of the cortical glomerulus leading to cortical capillaries of small calibre (part of the cortical intertubular capillary network), and the large efferent vessel of the juxtamedullary glomerulus leading to medullary vessels of large calibre (the vasa recta)

part of the cortex. It will be seen further that it is the loop of Henle belonging to the nephron of the juxtamedullary glomerulus which alone passes into the inner zone (Whilst the glomerulus of the 'cortical nephron' shown in the figure is situated at the extreme periphery of the cortex, it will be appreciated that other nephrons have their glomeruli at deeper levels in

the cortex and that their loops of Henle project farther into the medulla than that of the nephron illustrated.)

Pai (1935) has shown that there is a further type of nephron (which we would include in our 'cortical' type) having a loop of Henle which does not descend into the medulla at all and which has no thin segment We have ourselves also seen such nephrons.

Huber (1935) gave measurements of the tubules, of which he had made complete dissections, using his maceration method. He classified the nephrons into three main types, distinguishing between those whose glomeruli were situated in the superficial, the intermediate, and the deepest zones of the cortex respectively His measurements show a surprising difference not only in the total lengths of the tubules of the three types of nephron, but also in the relative lengths of the individual segments. Most striking of all is the difference in the length of the thin segment of the loop of Henle, which in the case of a nephron arising from a glomerulus situated in the deepest zone of the cortex is 15·0 mm (in a total tubular length of 28 8 mm.), and in the case of a nephron arising from a glomerulus situated at the periphery of the cortex is 1·4 mm. (in a total tubular length of 20 5 mm).

The fact that individual nephrons differ so greatly in the proportions of the segments of which they are composed, and that this difference is associated

We are well aware that our studies are as yet far from complete, but the observations which we have been able to make are sufficient, particularly when linked with the work of Peter (1909) and Huber (1935), to suggest that there must be a fundamental difference in the functions of the cortical and juxtamedullary vasculo-nephric units.

We have no evidence that there is any difference in the vascular pattern of the capillary network surrounding the convoluted tubules of the cortical and juxtamedullary glomeruli The vessels, however, which lie adjacent to the other segments of the tubule, in particular to the loop of Henle, show a marked difference according to whether the tubule is one associated with a cortical or a juxtamedullary glomerulus In the former case the greater part of the loop of Henle lies in the cortex in a close-meshed capillary network (the cortical intertubular capillary network), whilst a shorter length lies in the outer part of the medulla This part of the tubule, which includes the very short length of thin segment of the loop of Henle (all that there is of this segment in this type of nephron), lies amongst the vessels of the vasa recta system (see Figure 53) On the other hand, in the case of the tubule arising from the juxtamedullary glomerulus, a short length only of the loop of Henle lies in the cortex, surrounded by the cortical intertubular capillary network,

whilst the remainder of this *extremely long loop, which is composed almost* entirely of thin segment, lies in the medulla where the vessels adjacent to it are those of the vasa recta system.

Thus, it will be appreciated that the pattern of the vessels adjacent to the various segments of the tubules of the two main types of vasculo-nephric unit is *very different, the one being a close-meshed network of vessels of small* calibre, and the other mainly a system of vessels of large calibre grouped in radial bundles Further emphasis to these differences is given by the fact that the loop of Henle of the juxtamedullary vasculo-nephric unit, unlike that of the cortical one, passes deep into the medulla, even to the papilla, and that the greater part of this loop consists of the flattened epithelium which characterises the thin limb

Similarity of the vessels forming the by-pass through the medulla in the kidneys of man and of the rabbit

In our studies on the kidney of the rabbit we were able, by the use of various experimental procedures, to demonstrate a diversion of the intra-renal blood flow from the cortex through a medullary pathway. Further, we saw that this by-pass through the medulla was formed by the juxtamedullary glomeruli and their associated vessels Finally, we found that the juxta-medullary glomeruli and their associated vessels showed certain striking differences from the cortical glomeruli and their associated vessels.

In the human kidney we found that the vessels associated with the juxta-medullary and cortical glomeruli respectively showed differences no less striking than those seen in the rabbit.

1. The efferent vessel of the juxtamedullary glomerulus is of large calibre; it frequently exceeds even the afferent vessel in calibre. The efferent vessel of the cortical glomerulus is of small calibre; in comparison with the afferent arteriole of its glomerulus it is often minute.

2. The efferent vessel of the juxtamedullary glomerulus empties directly into straight medullary vessels of large calibre, the vasa recta (giving in addition small offshoots to a capillary network) The efferent vessel of the cortical glomerulus empties into a network of cortical capillaries of small calibre.

3. The vasa recta turn back towards the periphery at all levels of the medulla and particularly in its subcortical zone.

It will be seen, therefore, that the vascular channels associated with the juxtamedullary glomeruli of the human kidney are of such capacity that they must be able to carry blood which is diverted from the cortex, as we have seen that the corresponding vessels do in the rabbit. Functional evidence in support of our concept that the blood can be diverted from the cortex through a medullary pathway, such as the evidence which we had obtained by our

experiments on rabbits, was, for obvious reasons, not available in man. Nevertheless, in its application to the human kidney our concept gains strong

FIG. 55. Cortical glomer[illegible] (above) and juxtamedullary glomeruli (below) of kidneys of other ma[illegible] spe[illegible] ves[illegible] (Ph[illegible]

support from many physiological studies which have been made on human subjects, and from certain pathological conditions; the evidence from both of these sources will be discussed in Chapter VII

III KIDNEYS OF OTHER ANIMALS

The minute vascular pattern of the kidneys of the dog, cat, guinea-pig, and rat is essentially the same as that seen in the kidneys of man and of the rabbit. In all these animals the fundamental difference between the two types of glomeruli, cortical and juxtamedullary, is again clearly seen (Figure 55a)

The efferent vessel of the juxtamedullary glomerulus is relatively not as large in calibre in some of these animals as it is in the human kidney in which,

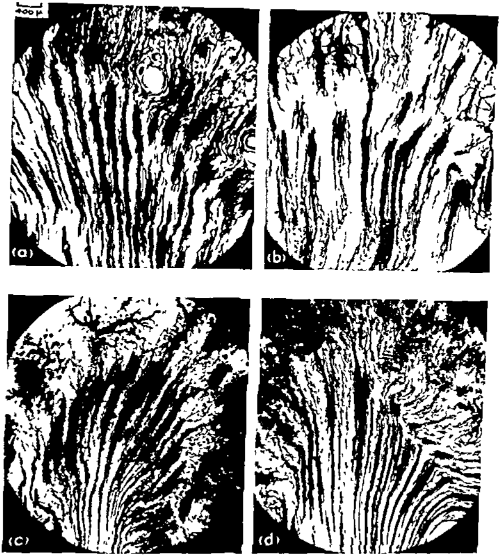

FIG 56 Sections of injected kidneys of various mammalian species, showing radial arrangement of bundles of vasa recta in the medulla (a) dog (b) cat (c) rat (d) guinea pig (Photomicrographs at same magnification throughout)

as we have shown, it is often of larger calibre than the afferent arteriole of the same glomerulus; nevertheless, its calibre in all these animals greatly exceeds that of the efferent vessel of the cortical glomerulus.

The efferent vessels of the cortical and juxtamedullary glomeruli respectively

empty into vascular beds which show the same disparity in size and contrast in pattern as those which we have already described.

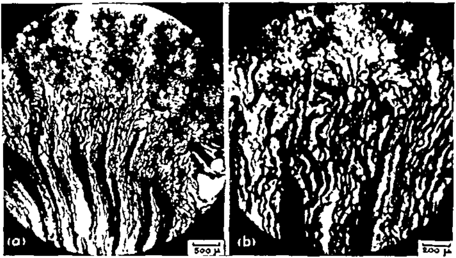

Fig 57 (*a*) Section of rat's kidney, injected via the renal vein, showing dense vascularity of subcortical zone of medulla. Note the contrast in size and pattern between the vasa recta in the medulla and the intertubular capillaries in the cortex (*b*) detail from centre of field of (*a*), showing complex arrangement of vessels in subcortical zone

The vasa recta, taking their origin from the efferent vessels of the juxtamedullary glomeruli, pass into the medulla in similar compact bundles which show a radial arrangement strictly comparable with that seen in the rabbit (Figure 56) As in the kidneys of both man and the rabbit, these bundles show a progressive diminution in the number of their constituent vessels as they pass towards the medullary papilla

The loops in the vasa recta responsible for this diminution are seen again at all levels of the medulla and the dense vascularity in the subcortical zone is clearly apparent, the complex arrangement of the vessels in this region being particularly striking in the rat (Figure 57)

It will thus be seen that the characteristic features of those channels which in the rabbit were shown to constitute the medullary by-pass for blood diverted from the cortex, namely, the vessels associated with the juxtamedullary glomeruli, are not only present in the human kidney, but are also evident in the kidneys of the dog, cat, guinea-pig, and rat.

DEGENERATIVE CHANGES IN JUXTAMEDULLARY GLOMERULI

In some of our material we have observed that many of the juxtamedullary glomeruli present an unexpected picture With the stereoscopic microscope

and high power objectives, examination of neoprene casts of the *normal* glomerulus, of both the juxtamedullary and the cortical types, shows two distinct vascular trunks entering and leaving the glomerulus side by side. Often the exact origin of these trunks is obscured by the interwoven capillaries of the tuft, but in many cases it has been possible to see that the design of the glomeruli of both types follows a uniform plan. The afferent arteriole divides into two or more main branches, which often partially embrace the emergent efferent glomerular vessel, and these branches rapidly subdivide to form the superficial capillaries of the glomerulus. These capillaries then pass towards the centre of the tuft where at some point they rejoin to form the efferent vessel, which emerges from the depths of the closely packed mass of capillaries.

Early in our studies of human kidneys we found juxtamedullary glomeruli which were a mere travesty of the normal type. The afferent and efferent trunks of the abnormal glomerulus formed a continuous vessel of large calibre which was plainly visible throughout its length, being in no way obscured by the capillaries of the tuft. This vessel generally had a bend in it, often a sharp one, opposite the centre of the glomerulus, and distal to this bend the calibre of the vessel was the same as before or even greater. Attached to the convex side of the bend were pathetically inadequate capillary loops.

As we studied more and more material it became clear that these abnormal types of glomeruli were not merely rare freaks. In the kidneys of elderly persons and of those suffering from certain pathological conditions we found many of these deformed glomeruli, and, moreover, we saw so many varieties in the degree of deformation that we came to the conclusion that in these strange glomeruli we were seeing the results of a progressive degenerative process.

In Figure 58 we reproduce a selection of juxtamedullary glomeruli to illustrate the progress of degeneration. Figure 58*a* shows a normal juxtamedul[illegible] In the early stages of degeneration (Figure 58*b*), a casual [illegible], that it is of normal type, but on closer [illegible]ion, it is seen that the afferent and efferent vessels [illegible]t, short trunk of a calibre equal to their own, which is partly buried in the glomerular tuft. In some cases (see Figure 59*a*) an apparently normal, well-formed glomerulus is seen attached to the side of an almost straight vessel, a continuous 'afferent-efferent' trunk. In later stages (Figure 58 *c* to *h*), however, the glomerulus becomes progressively more deformed, the number of capillary loops diminishing and forming mere appendages of the continuous 'afferent-efferent' trunk. In a still more advanced stage of degeneration (Figure 58*i*) the capillary loops, which are usually attached to the convex side of the bend, themselves disappear, and all that remain to represent the glomerulus are a

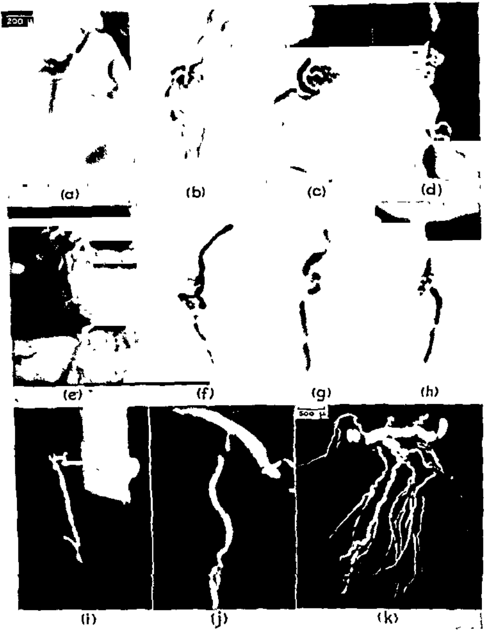

FIG. 58 Neoprene casts from human kidneys, illustrating the progress of degeneration of juxtamedullary glomeruli. In each case the afferent arteriole is above and the efferent vessel below. (*a*) normal juxtamedullary glomerulus. (*b*) to (*i*) juxtamedullary glomeruli in various stages of degeneration. (*j*) and (*k*) 'arteriae rectae verae'. For further details see text. (Photomicrographs (*a*) to (*j*) at same magnificatio

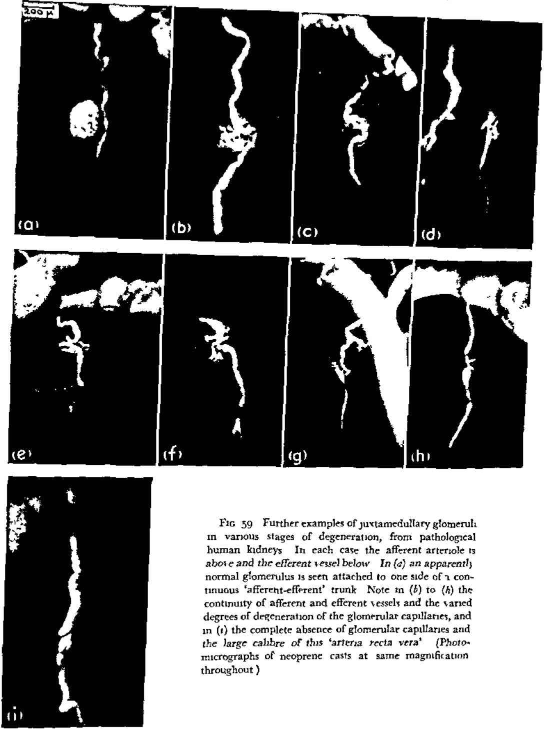

FIG 59 Further examples of juxtamedullary glomeruli in various stages of degeneration, from pathological human kidneys In each case the afferent arteriole is above and the efferent vessel below In (a) an apparently normal glomerulus is seen attached to one side of a continuous 'afferent-efferent' trunk Note in (b) to (h) the continuity of afferent and efferent vessels and the varied degrees of degeneration of the glomerular capillaries, and in (i) the complete absence of glomerular capillaries and the large calibre of this 'arteria recta vera' (Photomicrographs of neoprene casts at same magnification throughout)

few twig-like projections at the site of the bend in the continuous 'afferent-efferent' vessel. Lastly (Figure 58*j*, *k*; see also Figure 59*i*), even these vestiges of the glomerulus vanish, and all that is left is the continuous 'afferent-efferent' vessel, in which the original site of the glomerulus can often be recognised by the characteristic bend. *This we consider to be the explanation of the origin of the vessels known as 'arteriae rectae verae'*, whose existence has been a matter of considerable dispute, and which we believe to occur only as a result of a [illegible] vessel.

We believe that similar degenerative changes may account for the occurrence of the so-called Ludwig's (or Isaacs-Ludwig's) vessel. In Figure 60 we show an 'arteria recta vera' which has the characteristic bend [illegible] glomerulus of cortical type Thus, before the degeneration of the juxtamedullary glomerulus the afferent vessel of this glomerulus and that of the adjacent cortical glomerulus sprang from a common short trunk (a not uncommon arrangement). If these two glomeruli had been situated more peripherally in the cortex, instead of near the base of an interlobular artery, both would have been glomeruli of cortical type, and the efferent vessel of the degenerate glomerulus would have joined the cortical intertubular capillary network instead of dividing into vasa recta. In these circumstances, the continuous 'afferent-efferent' trunk resulting from the degeneration of the glomerulus would, we believe, have formed a Ludwig's vessel

FIG 60 'Arteria recta vera' of human kidney (photomicrograph of neoprene cast) Note sharp bend at site of vanished juxtamedullary glomerulus The afferent arteriole [illegible] glomerulus sprang from a common trunk

Because of the special advantage which specimens injected with neoprene afford in permitting manipulation and dissection of the casts, we have learnt more about these abnormal glomeruli by the use of this injection mass than by any other method of study Sometimes when we have dissected the cast of a seemingly normal juxtamedullary glomerulus we have seen what appears to be the first stage in the progress of degeneration. In addition to the normal capillary loops there is one much dilated capillary, uniting the afferent and

efferent vessels. Figure 61 shows the striking difference in size between this junctional vessel and the adjacent glomerular capillary loops.

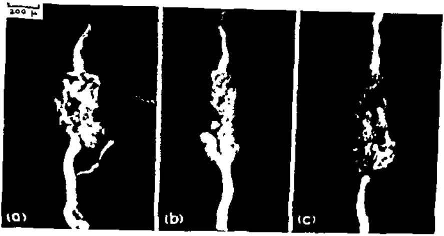

FIG 61. Photomicrographs of a neoprene cast from a human kidney, showing a juxtamedullary glomerulus in an early stage of degeneration (*a*) and (*b*) are two views of the glomerulus after partial dissection, showing a dilated glomerular 'capillary' uniting afferent and efferent vessels (*c*) another view of the same glomerulus, somewhat stretched out and after further dissection, showing the great difference in calibre between the dilated 'capillary', uniting afferent and efferent vessels, and the other capillaries of the glomerular tuft Note that the efferent vessel (below) is of larger calibre than the afferent vessel (above)

We have found glomeruli of this abnormal type not only in human kidneys, but also occasionally in those of the rabbit, the rat, and the cat (Figure 62). So far we have seen the degenerative change affecting the juxtamedullary glomeruli far more frequently than the cortical glomeruli, although degenerative changes have been found among the latter.

Since first observing degenerate forms of glomeruli in our material we have given much thought to the problem of their evolution, for we realised that when this abnormality is present in the case of a juxtamedullary glomerulus it must have a special significance. As we have already shown, the normal juxtamedullary glomerulus, with its large efferent vessel leading directly to the vasa recta system, must be able, in ordinary circumstances, to carry a much larger flow of blood than a cortical glomerulus This fact must in itself be of profound significance to the function of the juxtamedullary glomerulus But in the case of an abnormal juxtamedullary glomerulus of the type described, when the blood flow passes directly from the afferent arteriole to the efferent vessel without the interposition of glomerular capillaries, this significance becomes even more pronounced, for an even greater quantity of blood may now pass to the vast vascular bed of the vasa recta system in the medulla. It is obvious that these degenerating juxtamedullary glomeruli and, still more, the 'arteriae rectae verae', which are the end result of this

degeneration, when they are present in large numbers, must *profoundly affect the distribution of the intrarenal blood flow*. For in such cases these vessels provide

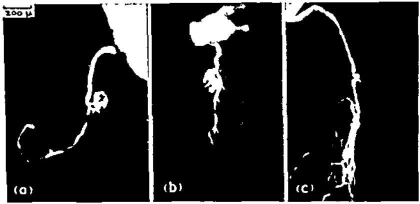

FIG 62 Degenerate juxtamedullary glomeruli from the kidneys of (*a*) a rabbit, (*b*) a rat, and (*c*) a cat In each case the afferent and efferent vessels form a continuous trunk (compare with Figures 58, 59) In (*c*), the structure has almost reached the stage of being an 'arteria recta vera', the characteristic bend at the site of the glomerulus being well seen (Photomicrographs of neoprene casts all at same magnification)

not only a larger but an easier pathway through which the blood may be diverted from the cortex.

Evolution and significance of degenerate juxtamedullary glomeruli

We believe that the glomeruli which show the earliest stages of the degenerative change, such as that seen in Figure 61, provide a clue to the problem of the evolution of the degenerate juxtamedullary glomerulus. As we interpret it, the excessive operation of the mechanism by which blood is diverted from the cortex through the medullary by-pass causes an initial dilatation of one of the capillary loops of the juxtamedullary glomerulus, probably a loop that is shorter and broader than the others. When the by-passing mechanism next operates, this dilated capillary carries more of the glomerular blood flow than any other capillaries of the glomerulus, and in consequence becomes even more dilated, to carry still more of the glomerular blood flow when the by-passing mechanism next operates This sequence of events, frequently repeated, leads inevitably to a final, permanent, gross dilatation of the affected capillary, and at the same time to the atrophy of all the other capillary loops of the glomerular tuft.

In this final stage, the afferent and efferent vessels, united by a grossly dilated 'capillary', form a single continuous trunk of large calibre (see Figures 58*j*, *k*, 59*i*, and 60), and thereby provide a direct and wide pathway to the

vasa recta. Consequently, the channels forming the medullary by-pass now of necessity carry a very great and continuous flow of blood, depriving the cortex of much of its circulation, and the delicate adjustments between the cortical and medullary circulations which we believe to occur in normal kidneys (see Chapters V and VI) are profoundly disturbed. The effects of this disturbance will be discussed in Chapter VII.

In a study of animal material, MacCallum (1939) found glomeruli in varying degrees of degeneration, and his detailed account and drawings of the degenerating glomerulus correspond very closely with our findings. We agree with his conclusions that the mammalian renal blood supply is normally exclusively glomerular, and that aglomerular vessels, wherever they occur, are either intermediate or end stages of a pathologically induced series of circulatory readjustments, and are thus pathological deviants from the normal pattern.

Oliver (1939) has demonstrated readjustments of an essentially similar type in the vascular pattern of the human kidney in Bright's disease, though he postulates the presence of a few vessels passing directly to the intertubular capillary network as a normal finding, and also shows that new direct vessels develop in inflammatory granulation tissue. Loomis (1936) and Loomis and Jett-Jackson (1942) have described changes similar to those which we have seen and described above in glomeruli around arteriosclerotic scars in human kidneys, and also in the edge of infarcts produced experimentally in the kidneys of rats, and have stressed the lability of capillary channels whose enlargement and regression they have shown to occur so readily in response to local and general changes in haemodynamics. In their classical experiments on the rabbit's ear, Clark and Clark (1932, 1935) have studied similar capillary changes by direct vision.

Wilmer (1941), using the celloidin corrosion technique, made a detailed investigation of the glomeruli of human kidneys, but he did not find any glomerulus of this type among the hundreds examined. In this he agreed with Vimtrup (1928) whose careful studies provided much of the basic knowledge of the glomerulus. We are surprised that these two workers failed to find glomeruli of this degenerate type, and can only suggest that the material on which their observations were made was unusually free from the changes caused by age or disease.

We have discussed at some length the degenerate form of juxtamedullary glomeruli because we believe not only that they are, in the first instance, the direct result of diversion of the intrarenal blood flow from the cortex through the medullary by-pass, but also that the degenerative process leads finally to a condition in which much of the intrarenal blood flow is permanently diverted through the channels of the medullary by-pass. The profound

pathological significance of this degenerative process in the case of the juxtamedullary glomeruli and its influence on the haemodynamics of the kidney are discussed in Chapter VII.

Summary of the Morphology and Implications of the By-pass through the Medulla

The object of the morphological studies which have been described in this chapter was to determine the vascular channels through which the intrarenal blood flow was carried when it was diverted from the cortex through a medullary by-pass

As a result of these studies we have been able to show that the vessels which constitute the medullary by-pass are those which are associated with the juxtamedullary glomeruli. That is to say, when the blood is diverted from the cortex through the medulla it passes in succession through the following channels:

1. The most proximal parts of the interlobular arteries.
2. The first branches of the interlobular arteries, that is, the afferent arterioles of the juxtamedullary glomeruli
3. The juxtamedullary glomeruli; that is, the glomeruli situated in the deepest zone of the cortex.
4. The efferent vessels of the juxtamedullary glomeruli, which lie partly in the cortico-medullary zone and partly in the subcortical zone of the medulla.
5. The 'arterial' components of the vasa recta, which lie in the medulla.
6. The loops of the vasa recta and, probably to a less extent, the intertubular capillaries which form part of the vasa recta system.
7. The 'venous' components of the vasa recta.
8. The proximal parts of the interlobular veins

Thus, the medullary by-pass is formed by channels the existence of which has been known to workers since the time of Bowman (1842), and which are present not only in the kidney of the rabbit, but also in the kidneys of other mammals, including man. We have seen that under certain conditions the juxtamedullary glomeruli undergo a degenerative process and that in consequence access to the medullary by-pass is facilitated.

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trast in the morphology of the respective nephrons which are associated with the juxtamedullary and cortical glomeruli and thus with the medullary and cortical circulations of the kidney.

In view of these morphological differences in both the vascular and the tubular elements of the vasculo-nephric units which are associated with the medullary and cortical circulations respectively, it is impossible to escape the conclusion that the juxtamedullary and cortical vasculo-nephric units do not function in an identical manner

Finally, the proximity of the vessels of the vasa recta system, which constitute by far the greater part of the medullary pathway, to the medullary portions of all loops of Henle (including their thin segments), where these lie in the medulla, suggests that the medullary circulation is closely related to the functions of these parts of the tubules. This will be referred to again in Chapters VI and VII.

CHAPTER V

Studies of the Cortical and Medullary Circulations

THE angiographic records described in Chapter II were made in a study directed mainly to the behaviour of the renal artery and vein under normal and experimental conditions. During that part of the investigation our attention was drawn to the circulation within the kidney itself by the observation that fundamental changes might occur in the intrarenal circulation. As described in Chapter III, we found that the intrarenal blood flow, which in normal circumstances passes mainly through the cortex, might in some conditions be diverted from the cortex through a medullary pathway. As a result of our anatomical studies described in Chapter IV, we learned that the channels through which the blood flow is directed when it is diverted from the cortex are the vessels associated with the juxtamedullary glomeruli. These last studies had also shown that the vessels which form the medullary pathway are very different in size and pattern from the vessels which form the cortical pathway.

Thus, our various studies had by this stage given us a considerably increased understanding of the structures of the kidney and of its circulation, both in the normal animal and in animals subjected to various experimental procedures. Taking advantage of our knowledge of the possibilities of changes in the intrarenal blood flow, we next carefully re-examined our angiographic material to see whether it showed any evidence of a redistribution of the intrarenal circulation We found that it undoubtedly did show such evidence. In many cases, however, although the distribution of the intrarenal blood flow seen in animals submitted to certain experimental procedures differed from that seen in normal animals, the difference was slight and the alteration in the flow transient. In further experiments, therefore, we tried to produce changes of intrarenal distribution which were more marked and of longer duration, and to show that, on occasion, the circulation through the kidney might be almost exclusively cortical or almost exclusively medullary.

In this chapter we discuss the data obtained from the re-examination of our earlier angiographs and the information derived from the further series of experiments

THE INTRARENAL CIRCULATION AS SEEN IN ANGIOGRAPHS

In the intact animal the visualisation of the finer vascular structures of an abdominal organ by means of angiography is, of necessity, very difficult.

The finer vessels of the kidney, for example, are so small that individually, when filled with contrast medium, they throw no visible shadow. However, when great numbers of these fine vessels in a particular region of the organ are filled with contrast medium, they cast a diffuse shadow, which, in favourable circumstances, is clearly seen to be heavier than the shadows of neighbouring regions in which fewer vessels are filled The circumstances are, however, seldom as favourable as one could wish in animals with an intact abdomen, because of the many superimposed structures. The overall background against which the kidney is seen is frequently extremely uneven in density. There may be shadows due to contrast medium in the vessels of superimposed tissues; there may be shadows of unequal density due to differences in thickness of the various superimposed tissues; above all, there may be extreme variations in the density of the background as a result of the different contents of various parts of the intestines overlying the kidney. The presence of uneven gas shadows in the intestines, which so often makes difficult the interpretation of abdominal radiographs in clinical work, has frequently been a serious obstacle to our study of the intrarenal distribution of contrast medium in the intact experimental animal.

Notwithstanding all these difficulties, it has been possible in many of our angiographs to see variations in the density of the shadow in different zones of the kidney. The difference in density is often slight and may be partly masked by superimposed shadows; further, although an increased or decreased density in one zone may be obvious in the original film, it becomes less apparent or may even be indiscernible in a print made from the film Any further processes which are necessary for reproduction result in a still further loss of definition.

It is because of all these technical difficulties that, although the observations which we describe in this chapter are based on the examination of hundreds of the original films, we have selected only a very small number of these angiographs to accompany the text. We hope that, despite losses in reproduction, they will illustrate our points, like all the rest of our figures they have not been retouched in any way.

I. DISTRIBUTION OF CONTRAST MEDIUM IN THE CORTEX AND MEDULLA OF THE NORMAL KIDNEY

In the re-examination of our angiographic material for the purpose of studying the distribution of contrast medium within the kidney, we turned first to the angiographs of normal animals. We found that in really good films, exposed at appropriate intervals, four distinct stages could be seen in the

(a) (b) (c) (d)

and the shadow in the subcortical zone is less clearly defined The renal artery is empty and the maximum concentration of the contrast medium is passing to the renal vein

(*a*) and (*c*) serial angiographs of one rabbit, (*b*) and (*d*) serial angiographs of another rabbit (see text for technical reasons necessitating use of two animals for this series)

passage of the contrast medium from the renal artery to the renal vein. These stages are illustrated in Figure 63 and may be described as follows:

First stage (early arterial) The contrast medium is seen filling the renal artery and its intrarenal branches; it has not yet reached the cortex in any quantity and the kidney shows a light and uniform shadow (Figure 63*a*)

Second stage (late arterial). The contrast medium is seen to be chiefly in the cortex, the renal artery is beginning to empty, and the renal vein is beginning to fill (Figure 63*b*).

Third stage (early venous) The densest shadow is now seen to be in the medulla, and particularly in its subcortical zone, only a trace of contrast medium is left in the renal artery, and the renal vein, together with its main tributaries, is well filled (Figure 63*c*).

Fourth stage (late venous) The amount of contrast medium in the medulla is reduced, and the shadow in the subcortical zone is less clearly defined; the renal artery is now empty and the densest shadow is seen in the renal vein (Figure 63*d*)

The rapidity with which the first three stages of the intrarenal circuit succeed each other has so far made it difficult, for technical reasons, to record with one injection two of these three characteristic stages consecutively. The transition from the third to the fourth stage occurs more slowly and

there is thus sufficient time to obtain in two radiographic exposures both an early and a late venous picture after a single injection of contrast medium.[1] Since the circulation through the kidney is continuous and the stages described are merely momentary phases in this circulation, it will be obvious that our angiographic material shows many examples of stages intermediate between the four described The difference of a mere fraction of a second in the interval between the injection of contrast medium and the exposure of the film makes a considerable difference in the precise stage recorded. The angiographs showing these intermediate stages, although presenting a less striking picture, provided the links between the four main stages illustrated in Figure 63.

It must be pointed out that for the purpose of determining the stage of the intrarenal circuit in any given angiograph the assessment is not based on the time interval between the injection of the contrast medium and the taking of the radiograph, for this interval had to be specially adjusted in certain experiments to allow for an altered speed in the systemic circulation, indeed, we found that this speed is subject to some variation even in a normal animal. Instead, the stage is assessed from the location of the densest shadow, and by the interrelation of the shadows seen respectively in the renal artery, the cortex, the medulla, and the renal vein. Further evidence for this assessment is provided by the stage of progress of the column of contrast medium in the other vessels, from the heart to the vessels of the hind limbs (the field covered by our radiographs).

Our interpretation of the differential distribution of contrast medium in the various stages of its intrarenal circuit is as follows. *In the first place, we* assume that the course taken by the contrast medium[2] through the kidney is identical with the course taken by the blood. *In the normal animal the* greater part of the intrarenal blood flow circulates through the cortex, and a smaller proportion passes through the medulla, *by way of the juxtamedullary* glomeruli and their associated vessels, particularly those of the vasa recta system (see Chapter IV). We believe *that the abundant and rapid cortical blood flow* accounts for the characteristic shadow in the cortex in the later arterial stages; that is to say, in *the first stages in which the kidney* shows a heavier shadow in one zone than in another (Figure *63b*) *We believe* also that the relative absence of shadow in *the cortex in the* venous stages of the intrarenal circuit (Figure *63c, d*) is due to the factor of rapid cortical blood flow; in other words, that *the absence of cortical* shadow is due to the

copious flow of non-opaque blood which follows immediately behind the column of contrast medium.

The heavier shadow of the medulla in the venous stages of the intrarenal [illegible] are, we think, due to a *relatively* [illegible] The characteristics of the vessels [illegible] escribed in Chapter IV, support the view that in normal circumstances the flow through these channels is slow as compared with the flow through the vessels of the cortex. For the vessels of the vasa recta system exist in great numbers and they are mainly of large calibre. The profuse numbers and large calibre of these vessels are particularly striking on the venous side of the vasa recta system in the subcortical zone of the medulla, immediately prior to their terminations in the collecting veins, and the heavy shadow of the subcortical zone seen in the venous angiographs (see Figure 63*c*) is probably due to the location of the contrast medium in these vessels at this stage of its intrarenal circuit. A further indication that the flow through the medullary channels is normally relatively slow is provided by the fact that the vessels of the vasa recta system empty into vessels which drain in common both cortex and medulla; consequently, in normal conditions, when the collecting veins are already carrying the great outflow from an active cortex, the outflow from the medulla may well be delayed. Thus, all the evidence at our disposal indicates that in normal circumstances the circulation through the medulla is relatively slow as compared with the circulation through the cortex, and explains why the characteristic shadow of the medulla appears later and clears more slowly than does the shadow of the cortex.

II. CHANGES IN INTRARENAL DISTRIBUTION OF CONTRAST MEDIUM AFTER VARIOUS EXPERIMENTAL PROCEDURES

In studying the angiographs of animals submitted to experimental procedures, we found that in many cases the distribution of contrast medium at certain stages of its intrarenal circuit was different from that seen in the normal animal Two fundamental differences were seen, and the experimental procedures which caused the altered distribution may therefore be classified, according to their effects, in two groups:

(*a*) Those causing an increase in the density of the cortical shadow and a decrease in the density of the medullary shadow, as compared with the shadows seen in the normal animal.

(*b*) Those causing a decrease in the density of the cortical shadow and an increase in the density of the medullary shadow, as compared with the shadows seen in the normal animal

As has been shown above, in the *normal* animal the cortex throws a heavier

shadow than the medulla in the later arterial stages of the intrarenal circuit, and the medulla throws a heavier shadow than the cortex in the venous stages of the circuit. Thus, in determining any deviation from the normal distribution of contrast medium in the cortex and the medulla respectively in animals subjected to experimental procedures, it is essential first of all to assess the stage of the intrarenal circuit represented in the angiograph studied. In other words, one must determine by the presence or by the density of the shadows in the renal artery and vein respectively (together with the point reached by the head or the tail of the column of contrast medium in the vessels of the systemic circulation elsewhere in the body) whether the stage represented is arterial or venous. Having determined by the correlation of these various shadows the stage of the intrarenal circuit shown in the angiograph, one can then decide whether or not the density of the shadows in the cortex or medulla shows any deviation from the normal. For example, since in the normal animal the cortex throws a heavier shadow than the medulla only in the later arterial stages (Figure 63*b*), a decreased cortical circulation with a correspondingly increased medullary blood flow can only be satisfactorily demonstrated by a decreased cortical shadow at these later arterial stages of the intrarenal circuit. Similarly, since in the normal animal the medulla throws a heavier shadow than the cortex only in the venous stages of the intrarenal circuit (Figure 63*c*, *d*), a decreased medullary circulation, with a correspondingly increased cortical blood flow, can be satisfactorily demonstrated only in angiographs showing the venous stages.

(*a*) *Increase in cortical shadow with decrease in medullary shadow*

Although it was not a constant effect, an increased shadow in the cortex and a decreased shadow in the medulla were seen after the administration of *pilocarpine*. For the reasons which have just been described, the difference from the normal animal is best seen in angiographs recording the venous stages of the intrarenal circuit of the contrast medium.

In the normal animal, as we have shown above, at the early venous stage the densest shadow of the contrast medium is seen to be in the medulla, particularly in the subcortical zone. After an intravenous injection of pilocarpine the densest shadow at the early venous stage may be seen to be in the [illegible]

supply to the cortex is in these cases even greater than usual, and that medulla less than usual. More contrast medium is seen in the renal artery than is usual at this stage of the intrarenal circuit, and this fact supports our interpretation that the increased cortical shadow seen in these angiographs is due to a dilatation of the cortical vessels resulting from the pilocarpine

injection, with a consequent reduction in the cortical speed of flow. Pilocarpine causes a similar dilatation of peripheral vessels elsewhere in the body.

This observation and its interpretation suggest one possible explanation of the failure of Claude Bernard (see Bernard, 1858 *a*, *b*, 1859) to correlate in all circumstances urine formation with the appearance of red blood in the renal vein (see Chapter III), which to him was an indication of dilated capillaries. For in the case of pilocarpine the peripheral vasodilatation elsewhere in the body suggests a lowering of the general blood pressure and a consequent fall in the rate of glomerular filtration.

The most striking examples, however, of the type of change in which the cortical shadow was increased and the medullary shadow decreased, were obtained from another group of experiments, in which the *splanchnic nerves had been divided before a tourniquet was applied to the thigh.* In these experiments the splanchnic nerves of several rabbits were divided bilaterally and a period of five weeks was allowed to elapse so that degeneration should occur in the nerves and in their terminations Then control angiographs were made of each animal, after which a tourniquet was applied to the left thigh, and further angiographs were made both while the tourniquet was in position and also after its removal.

The results of this group of experiments seemed to us of great significance. The first angiographs, made before the application of the tourniquet, showed the normal sequence of stages in the passage of the contrast medium through the kidney (Figure 64*a*, *c*) The later sets of angiographs, made while the tourniquet was in position and also after it had been removed, showed not only a marked difference from the first set of angiographs of the same animal, but also a striking contrast to the later sets of angiographs of animals belonging to the ordinary tourniquet series (described in Chapter II and also below), that is, those with their splanchnic nerves intact In these later angiographs of tourniquet animals with divided splanchnic nerves, the shadow of the contrast medium is seen already in the cortex at the early arterial stage of its intrarenal circuit (Figure 64*b*), and it remains in the cortex exclusively throughout the arterial and venous stages In the venous stages the dense shadow in the cortex is in marked contrast to the striking and unusual absence of shadow in the medulla (Figure 64*d*).

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there

two types of experiment, there is also a striking difference in the calibres of the vessels elsewhere in the body In the case of the pilocarpine experiments, the presence of contrast medium in the renal artery at the venous stage of its intrarenal circuit was considered as a further indication that the increased

cortical shadow was due to the effect of this drug as a peripheral vasodilator. But, in the case of the experiments in which a tourniquet was applied after previous division of the splanchnic nerves, the vasodilatation appeared to be limited to the renal cortex. The renal artery, although not actually dilated, did not undergo the marked constriction seen in tourniquet animals with their splanchnic nerves intact, and thus demonstrated to a lesser extent the same behaviour as the cortex, but the angiographs show that on the vessels elsewhere in the body the application of the tourniquet had had its usual effect; in other words, all the other vessels (with the usual exception of the mesenteric artery) were markedly constricted. Clearly, therefore, the division of the splanchnic nerves had interfered with the mechanism which controls the vessels of the kidney, and particularly those of the cortex, and these vessels had been subjected to an increase in central blood pressure due to the peripheral vasoconstriction elsewhere in the body. In support of this interpretation, we found that the angiographs of these animals which were made before the tourniquet was applied showed a distribution of the contrast medium within the kidney resembling that seen in the normal animal (Figure 64*a*, *c*). It was only in the angiographs made while the tourniquet was in position and also after it had been removed, when peripheral constriction

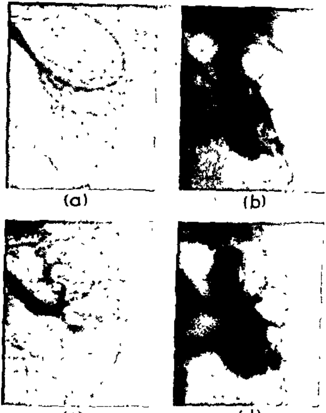


FIG 64 Angiographs of a rabbit whose splanchnic nerves had been divided five weeks previously. (*a*) and (*c*) serial angiographs

those seen in (*a*) and (*c*), the shadow of the cortex is more dense than that of the medulla The difference from the normal is particularly well seen in (*d*), the venous stage, when normally the cortex is poorly filled whilst the shadow of the medulla is conspicuous. Compare (*d*) with (*c*) and also with Figure 63 *c* and *d*.

64*b*, *d*). These results were consistent in the whole group of animals in which the splanchnic nerves were divided prior to the application of a tourniquet to the thigh.

As has already been pointed out in Chapter II, the animals in which the splanchnic nerves had been divided before a tourniquet was applied provided the only exceptions to a finding which had otherwise been invariable in our experiments; namely, that the renal and femoral arteries show a parallel response to traumatic procedures. The difference in the effect on the cortical circulation produced by the application of a tourniquet in animals whose splanchnic nerves had been divided, and in those whose splanchnic nerves were intact, was no less striking than the difference in the behaviour of the renal artery in these two groups of animals, and will be appreciated after a reconsideration of the angiographs of the tourniquet animals with splanchnic nerves intact.

(*b*) *Decrease in cortical shadow with increase in medullary shadow*

A good example of an angiograph showing a decrease in cortical shadow with a corresponding increase in the shadow of the medulla will have already been seen in Figure 20. This example was described in and reproduced as one of the figures accompanying the text of Chapter III because it served to illustrate the effects of certain drugs which we described in that chapter and which we had recorded mainly by visual observations of the exposed kidney

The angiographic records of the *tourniquet* experiments, as has already been indicated in Chapter II, provided us with the first suggestion that there might be an alteration in the course of the intrarenal blood flow. We have shown above that, in angiographs of normal rabbits, certain definite stages can be seen in the passage of the contrast medium through the kidney, and that the location of the densest shadow within the kidney bears a constant relation to a specific stage in the intrarenal circuit (see Figure 63). In angiographs of rabbits made while a tourniquet was in position on the thigh or after its removal, it was seen that the normal sequence of events was altered Apart from the reduction in calibre of the renal artery, described in Chapter II, there were four other striking features to be seen in the angiographs of these rabbits:

1 The poor shadow in the cortex of the kidney.
2 The early appearance of a shadow in the renal medulla.
3 The early appearance of a shadow in the renal vein.
4. The late clearance of the shadow from the renal artery.

These features became increasingly apparent the greater the interval of time between the application of the tourniquet and the making of the angiograph.

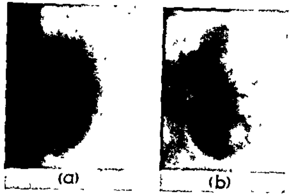


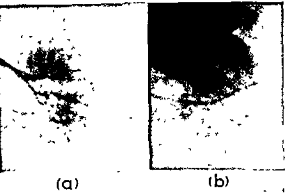
Fig 65 (*a*) Angiograph showing cortical ischaemia in a tourniquet rabbit (with splanchnic nerves intact) The tourniquet had been applied to the left thigh for 1½ hours, and the angiograph was made 80 minutes after its removal. (*b*) Angiograph of normal rabbit for comparison Both angiographs show late arterial stage of intrarenal circuit of contrast medium Note in (*a*) the poor shadow of the renal cortex and the heavier shadow of the medulla, contrasting with the good cortical shadow and poor medullary shadow seen at a corresponding stage in the normal animal (*b*)

The most conspicuous differences from the normal angiograph are the relative *absence of shadow in the cortex* at any stage of the circuit of contrast medium through the kidney, and the presence of a correspondingly *increased shadow in the medulla* throughout all stages of the circuit. In some of our experiments, the final angiographs were made while there was a certain amount of contrast medium from the previous injection still circulating in the blood, and in these angiographs the medullary shadow is a permanent feature. This shadow in the medulla becomes denser as a result of the new injection, but as the cortex shows no increase in shadow the contrast between the filled medulla and the almost empty cortex becomes more striking (Figure 65*a*). The distribution of the shadow in these angiographs shows that the contrast medium is taking a medullary rather than a cortical route.

The early appearance of the shadow in the renal vein was one of our first indications of the existence of an intrarenal short-circuiting mechanism, for it suggested to us that the head of the column of contrast medium was taking a shorter course than usual through the kidney (see Chapter II). The diminished density of the cortical shadow and the increased medullary shadow in these same angiographs—changes in the intrarenal circulation which were only fully appreciated at a later stage in our studies—supported the evidence which had already been derived from other sources that the pathway of the 'short-circuit' was through the medulla. The late emptying of the renal artery seemed to admit of two possible explanations. Firstly, a certain amount of contrast medium might be traversing a route longer than usual; that is, more of it than usual might be circulating through the vasa recta to the extreme apex of the papilla, this being obviously a relatively long route. Secondly, the total vascular bed of the pathway traversed might be smaller than usual, an explanation which is supported by the fact that the arterial components of the medullary pathway are very much fewer in number,

although larger in calibre, than the vessels which constitute the arterial components of the cortical pathway.

In our angiographic records of the effects of *sciatic stimulation* we were unable to detect any obvious change in the intrarenal circulation, but this absence of change may have been due to the fact that in all cases the angiographs were made after (and frequently a considerable period after) the conclusion of the stimulation and not while the stimulus was actually being applied Angiographs made after *stimulation of the distal end of the divided splanchnic nerve* gave a suggestion of a redistribution of intrarenal blood similar to that seen in the tourniquet animals, but were limited to one animal. Visual observations, however, of the exposed kidneys of animals subjected to stimulation of splanchnic and sciatic nerves showed that with both these procedures the blood supply to the cortex might be reduced (see Chapter III).



[illegible] the cortex and the increased shadow of the medulla

The angiograph reproduced as Figure 66*a* shows the reduced circulation through the renal cortex which may be seen after severe, rapid *haemorrhage.* Before this angiograph was made the rabbit, under nembutal and ether anaesthesia, had been bled quickly in successive stages until about one-third of its total blood volume had been removed. We found that after severe haemorrhage the speed of the circulation in general is considerably reduced and the time interval between the intravenous injection of contrast medium and the radiographic exposures must consequently be increased if the latter are to show the arterial and venous stages of the renal circulation The full length film, from which the detail of the left kidney shown in Figure 66*a* is taken, shows that the contrast medium has reached the popliteal artery. In normal animals the appearance of the contrast medium in so distant a part of the arterial tree coincides with the late arterial stage of the intrarenal circuit when the renal cortex is well filled (Figure 66*b*, see also Figure 63*b*). In the case of this animal, however, which had been bled, although the renal artery and its branches are filled, there is little shadow in the cortex of the kidney, and of the two regions, cortex and medulla, the medulla shows the heavier shadow.

bet

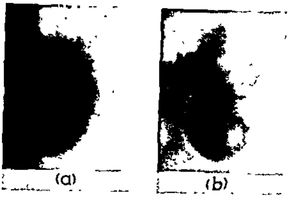


FIG 65 (*a*) Angiograph showing cortical ischaemia in a tourniquet rabbit (with splanchnic nerves intact) The tourniquet had been applied to the left thigh for $4\frac{1}{2}$ hours, and the angiograph was made 80 minutes after its removal. (*b*) Angiograph of normal rabbit for comparison. Both angiographs show late arterial stage of intrarenal circuit of contrast medium Note in (*a*) the poor shadow of the renal cortex and the heavier shadow of the medulla, contrasting with the good cortical shadow and poor medullary shadow seen at a corresponding stage in the normal animal (*b*)

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tion of the toxin, and in others after periods up to five days from the time when the toxin was given. In acute experiments on rabbits, in which the effects were studied mainly by direct observation of the exposed left kidney, the toxin was injected after the animal had been anaesthetised with nembutal and ether and a laparotomy had been performed. In other experiments the toxin was injected into unanaesthetised rabbits by an ear vein and later effects were studied under ether anaesthesia by direct observation of the exposed kidney, by angiographic records of the intact animal, and by injections of Indian ink The effects of the toxin at various times from its administration were also studied by microscopic examination of the kidneys both of animals in which an injection mass had been introduced and also of others without such an injection. In animals which were allowed to survive for more than a few hours after administration of the toxin, estimations were made of blood urea, blood proteins, and blood sugar both before and after the toxin was given, specimens of urine were also examined at the conclusion of the experiments

In general, the same experimental procedures and methods of study were used for rats as were used for the rabbits The only significant difference was that in rats injected with toxin for the purpose of studying its later effects the injection was made intraperitoneally instead of intravenously as in the rabbit

While the results of these experiments, obtained from the use of our special techniques and methods of study, have, we believe, opened up a new field in the assessment of vascular effects produced by *toxins*, only those aspects of the results which have a direct bearing on the diversion of the intrarenal blood flow from the renal cortex to the medulla were of immediate interest to us in our present studies

Immediate effects on the renal circulation of an injection of staphylococcus toxin

Examination of the exposed kidney showed that in susceptible rabbits its surface began to blanch within a few minutes of an intravenous injection of the toxin, and that thereafter the degree of pallor steadily increased It was noticeable that the colour of the blanched surface in these rabbits was greyish rather than the yellowish-white colour seen in the pallor produced by other experimental procedures. During the period of pallor, red streamlines could be seen in the renal vein (see Chapter III). We were so impressed by the effects seen in successful experiments that we quote a description which is taken almost word for word from the notes made at the time of one such experiment When the abdomen was opened, the surface of the left kidney and the blood in the left renal vein were seen to be normal in colour. Staphylococcus toxin was injected intravenously in the dosage of 0 2 ml. per kg. body

Because of the practical implications, the effects of haemorrhage present a problem of such far-reaching importance that it would obviously justify an investigation devoted exclusively to itself. For the purpose of our present studies, however, the rapid withdrawal of a considerable proportion of the total blood volume was merely one of a number of experimental procedures used with the object of effecting changes in the renal circulation. The wider aspects of this particular form of trauma must await a study at some future date.

III. PERMANENT DIVERSION OF BLOOD FLOW FROM CORTEX TO MEDULLA

The observations on the intrarenal circulation discussed up to this point were drawn mainly from angiographs of animals which have already been described from other aspects The experiments now to be described belong to a group which was designed with the object of producing a permanent diversion of the intrarenal blood flow from the cortex. In these experiments we used a wholly different method of causing the diversion, namely, the injection of *staphylococcus toxin*, and we recorded the effects not only by means of angiographs, but also by visual observations of the exposed kidneys and by the intravascular introduction of Indian ink and similar injection masses.

The idea of using staphylococcus toxin was suggested to us by the experimental work of De Navasquez (1938), who produced cortical necrosis of the kidney in rabbits by this agency. The staphylococcus toxin[1] with which we were supplied was approximately ten times as strong as that used by De Navasquez. We therefore used a dilution of one in ten of our toxin, so that our doses corresponded roughly with those of De Navasquez. The toxin was given by intravenous injection and in rabbits the dosage ranged from 0·1 to 0·5 ml. per kg. body weight Rats, which were also used in these experiments, were more tolerant than rabbits, and in these animals dosages ranged from 0·3 to 1·0 ml. per kg. body weight

We found that both rabbits and rats varied greatly in their susceptibility to the toxin[2] For example, two rabbits died within ten and twelve hours respectively after an injection in the dosage of 0·125 ml per kg. body weight, whereas two rabbits injected at the same time with the same batch of toxin, in the dosage of 0·15 ml. per kg body weight, showed no ill effects at this stage One of these latter animals was sacrificed at nineteen hours, and the other, which was allowed to survive, was alive and perfectly well many weeks later.

Observations were made in some animals immediately after administra-

[1] The toxin was kindly given to us by Dr A E Francis, of the Department of Bacteriology, Wellcome Physiological Research Laboratories

[2] *In these experiments we did not attempt* to estimate the presence of natural antitoxins to staphylococcus toxin in our animals

tion of the toxin, and in others after periods up to five days from the time when the toxin was given. In acute experiments on rabbits, in which the effects were studied mainly by direct observation of the exposed left kidney, the toxin was injected after the animal had been anaesthetised with nembutal and ether and a laparotomy had been performed. In other experiments the toxin was injected into unanaesthetised rabbits by an ear vein and later effects were studied under ether anaesthesia by direct observation of the exposed kidney, by angiographic records of the intact animal, and by injections of Indian ink. The effects of the toxin at various times from its administration were also studied by microscopic examination of the kidneys both of animals in which an injection mass had been introduced and also of others without such an injection In animals which were allowed to survive for more than a few hours after administration of the toxin, estimations were made of blood urea, blood proteins, and blood sugar both before and after the toxin was given; specimens of urine were also examined at the conclusion of the experiments

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weight. About one minute after injection of the toxin the surface of the kidney began to pale. One to two minutes later the blood in the renal vein began to darken. About seven minutes after the injection of the toxin a stream of brilliant red appeared in the caudal side of the vein. This stream was narrow at first, but it gradually increased in width until at approximately fifteen minutes from the time of injection it occupied the greater part of the vein, and the pulsatile flow of this stream could be clearly seen, contrasting with the apparently static condition of the adjacent darker blood in the vein. The surface of the kidney was still pale Little more than five minutes later the animal died.

In susceptible rats the immediate effects of an intravenous injection of toxin were similar to those seen in the rabbit, except that the surface of the kidney started to pale more rapidly, usually in less than a minute from the time of the injection of the toxin. At this stage the blood in the renal vein often reddened The cortical pallor seen in some rats was even more striking than that seen in rabbits, but the rats used in our experiments appeared on the whole to show an intense cortical pallor less consistently than a similar series of rabbits

Recordings of carotid arterial blood pressure in rabbits showed that the blanching of the surface of the kidney was not accompanied by any appreciable change in blood pressure. This finding was of particular interest in view of the marked rise in blood pressure which accompanies the blanching of the kidney surface after an intravenous injection of adrenaline in a high dosage, for it indicated that the blanching seen after an injection of staphylococcus toxin was due to a cause other than the liberation of adrenaline.

Later effects on the renal circulation of an injection of staphylococcus toxin

When applying our usual angiographic techniques to a study of the delayed effects of staphylococcus toxin in the intact animal, we encountered a serious obstacle to the production of satisfactory records. This obstacle took the form of great quantities of gas in the intestines which made it difficult to see the finer details of the renal vascular shadows in the angiographs. We decided, therefore, to supplement the series of angiographs made in the intact animal with a subsequent series made with the abdomen open and with the intestines drawn to one side to expose the left kidney.

A healthy rabbit with a blood urea of 29 mg. per cent was injected with staphylococcus toxin in the dosage of 0·15 ml. per kg. body weight. Twelve hours later the animal, which looked ill, [illegible] with ether, and a serial set of angiographs was made befor[illegible] the abdomen was opened, the intestines [illegible] left kidney, and a further set of angiographs was made forty-five minutes after

the previous set Finally, a quantity of contrast medium, twice as large as that normally given, was injected slowly so as to give a higher concentration in the blood, and at the conclusion of this injection the kidneys were quickly excised from the living animal and radiographed (Figure 67*a*).

A sample of blood taken at the end of the experiment, that is, thirteen hours after the injection of the toxin, showed a blood urea of 96 mg. per cent. The urine contained albumen in large quantity.

By a careful study of the first serial set of angiographs made in the intact animal it ... of the gas bubbles in the intestines, ... as no shadow of contrast medium i ... hough a definite shadow could be seen in the medulla The renal arteries were constricted, as also were the femoral arteries, and this experiment thus provided yet another example of the parallel behaviour of the arteries supplying the kidneys and the hind limbs respectively. The mesenteric artery was greatly dilated, a feature which again showed how different is the reaction of this vessel from the reactions of the renal and femoral arteries. The subsequent angiographs, made with the abdomen open, showed a marked medullary shadow which contrasted strongly with the absence of cortical filling.

The effect of the staphylococcus toxin on the kidneys of this animal is shown in Figure 67. Figure 67*a* is a radiograph of one of the kidneys which, as mentioned above, were excised shortly after the last of a series of injections of contrast medium made into the jugular vein during life. It will be seen that the medulla is extremely well filled; the outer two-thirds of the cortical zone show virtually no filling at all, and the remainder of the cortex, the deepest zone, while showing some degree of filling, has a less dense shadow than the medulla It is to be noted that the arteries are constricted. The photograph reproduced as Figure 67*b* shows a coronal section of the same kidney, and it will be seen that the greater part of the cortex is necrotic and that this zone corresponds with the unfilled zone of the cortex seen in the radiograph, Figure 67*a* The medulla, on the other hand, appears normal, and on microscopic examination its tissues were found to be living. Figures 67 *c* and *d* are radiomicrographs of sections of the same kidney and show in greater detail the course taken by the contrast medium in its circulation through the kidney. We see some of the main intrarenal arteries, the proximal parts of the interlobular arteries, juxtamedullary glomeruli (seen best in Figure 67*d*), and great numbers of well-filled vasa recta The radial arrangement of the bundles of vasa recta should be compared with the similar grouping of these vessels seen in Figures 23, 29, 31, and 56. The peripheral part of the cortex has clearly been excluded from the circulation, for all that can be seen are a few irregular withered-looking interlobular trunks, no glomeruli or intertubular capillary network being visible in this region. These trunks are seen to be mainly venous,

though an occasional one is clearly an interlobular artery, and we attribute this filling of some of the main cortical veins to a reflux from the vessels which

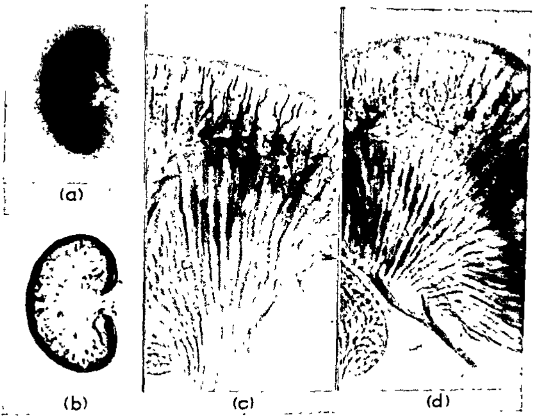


FIG 67 Kidney of rabbit with cortical necrosis, produced by intravenous injection of staphylococcus toxin An example of the continuous use of the medullary by-pass The contrast medium seen had been injected during life via the jugular vein, 13 hours after administration of the toxin

(*a*) Radiograph of excised right kidney Note that the peripheral two-thirds of the cortex have been excluded from the circulating thorotrast, but that the medullary vessels contain a great quantity of the contrast medium The arteries are constricted, the veins are well seen (*b*) photograph of coronal section of same kidney, showing dark, necrotic cortical zone corresponding with the unfilled peripheral zone seen in the radiograph (*a*), (*c*) and (*d*) radiomicrographs of sections of same kidney, showing details of vascular bed through which the contrast medium had circulated during life Note that contrast medium fills the proximal parts of interlobular arteries, juxtamedullary glomeruli and the vasa recta The withered-looking trunks extending towards the periphery of the cortex are mainly interlobular veins, probably filled by reflux of the contrast medium leaving the medullary pathway

drain the medulla, an explanation offered previously for similar findings described in Chapter IV. This filling of the cortical veins from a source other than the cortical glomeruli, in conditions in which the blood is diverted from the cortex to the medullary pathway, is a phenomenon which we have recorded after a number of different experimental procedures. The contrast between the necrosis of the cortex and the normal appearance of the medulla

blood

great
distension of the intestines with gas This feature was seen in all animals, both rabbits and rats, which were affected by the toxin but which nevertheless survived for some hours. The dilated mesenteric artery seen in the angiographs of the intact animal, combined with this distension and with the increase in the peritoneal fluid found on opening the abdomen, was strongly suggestive of an advanced degree of intestinal atony. In the animals most seriously affected by the toxin, the appearances at necropsy were those of a paralytic ileus. Confirmation of the great dilatation of the intestinal vessels which is a characteristic effect of this toxin was provided by the results of injections of Indian ink by the aorta. In these animals the degree to which the whole vascular bed of the intestines filled with ink was most surprising, the whole of these viscera becoming suddenly and intensely black and presenting an appearance seen in none of our previous experiments. This dramatic blackening of the intestines was in striking contrast to the virtually complete absence of staining of the surface of the kidneys (see Figure 69).

Visual observations of the appearances of the exposed viscera, before injection, revealed that the kidneys were enlarged and the surfaces of these organs were mottled (Figure 68). The blood vessels of the intestines were unusually prominent and red, and the intestines themselves were enormously distended with gas.

The results of another experiment of this group may be seen in Figures 69 and 70. The rabbit had been injected with staphylococcus toxin in the dosage of 0·15 ml. per kg. body weight. Sixteen hours later, when the animal had appeared ill for some hours and had a blood urea of 120 mg. per cent, it was anaesthetised with ether, the abdomen was opened, and an injection of Indian ink was made into the aorta by the method described in Chapter IV. As usual in this group of animals, the intestines became intensely blackened with the ink whilst, in striking contrast, the kidneys showed only a few punctate black spots on their pallid mottled surfaces (Figure 69) The appearance of the surface of this kidney should be compared with that seen in Figure 18*b*, which shows a similar lack of staining from an injected dye

FIG 68 Photograph of rabbit's kidney taken 12 hours after intravenous injection of staphylococcus toxin Note the mottled surface, which is characteristic of this stage in the development of cortical necrosis of the kidney

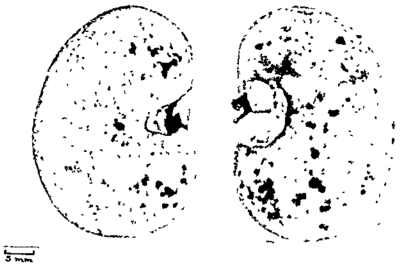
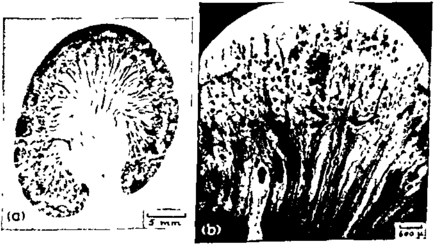


FIG 69 Photographs of a rabbit's kidneys showing cortical necrosis 16 hours after intravenous injection of staphylococcus toxin Indian ink had been injected during life via the aorta Note the few punctate black stains in the most pallid areas of the mottled surface



area a
that,
had been maintained through the medullary by-pass

after stimulation of the central end of the ipsilateral sciatic nerve. The cortical ischaemia demonstrated at the time of the injection of the dye in this latter animal was comparable with that present in the animal described above and which had resulted from an injection of staphylococcus toxin.

On section of the kidneys, the ink was seen to be present only in the deepest zone of the cortex and in the subcortical zone of the medulla The outer zone of the cortex, ranging from one-half to two-thirds of its width, was necrotic, showing a rather mottled pallor and being separated from the deeper zone by a narrow reddened line Beneath this line the narrow living zone of the cortex appeared normal or somewhat congested, as did also the medulla. No ink was seen in the necrotic part of the cortex, but the zone of living tissue deep to this and the subcortical zone of the medulla both showed the presence of the injection mass. All of the medullary tissues were living and the medullary vessels which were not filled with ink were filled with blood, showing that the whole medullary circulation was intact; indeed, the medulla appeared hyperaemic. The most striking features of sections of these kidneys when examined under the microscope were the ink-filled basal portions of interlobular arteries, juxtamedullary glomeruli, and vasa recta (Figure 70).

In the kidneys of animals susceptible to the toxin we had thus produced a *cortical ischaemia* of such a degree that it resulted in a cortical necrosis. The close similarity between the kidneys of these experimental animals, with their necrosis of the cortex and their living and hyperaemic medulla, and the kidneys of human cases showing bilateral cortical necrosis will be discussed in Chapter VII.

In studying the later effects of the injections of the toxin in rats, we found that these animals showed a variability in their susceptibility to the toxin quite as great as, if not greater than, that shown by rabbits. One example may be quoted in which the effects were pronounced The rat was injected intraperitoneally with staphylococcus toxin in the dosage of 0 3 ml. per kg. body weight. Twenty-four hours later, when the animal looked very ill, it was anaesthetised with ether and the abdomen was opened The intestines were greatly distended with gas and there was an excess of peritoneal fluid. The spleen was greatly enlarged and showed one purple raised area, a recent infarct. The liver was a mottled yellow. The intestines showed a few pale foci on the antimesenteric border The surfaces of both kidneys were markedly pale After a rapid inspection of the abdominal cavity, an injection of a few ml of Indian ink was made by hypodermic needle into the thoracic aorta, quickly exposed from the left side The result of this injection was most remarkable The stomach, the intestines, and the suprarenals immediately became intensely black, as did also the spleen, except for the infarct which remained a dark purple The kidneys, on the other hand, showed no staining of their surfaces; they remained pale throughout the experiment except for one or two small punctate black spots, although the ink had been seen

first in the renal artery and then in the renal vein, a fact which showed that it had made an intrarenal circuit. The liver remained a blotchy yellow, although a number of punctate black areas were seen on the surface. The whole picture was in striking contrast to that which is seen when Indian ink is injected into the thoracic aorta of a normal rat, when the surfaces of the kidneys are more deeply stained than the surfaces of any other abdominal organ.

Sections of the kidneys of this animal showed a poor filling of the renal vessels, but the vessels which contained the ink were those situated in the intermediate zone between cortex and medulla; on microscopic examination, the only glomeruli which had been filled with the injection mass were found to be the juxtamedullary glomeruli.

The pathological features of the cortical necrosis which can be produced in rabbits by means of staphylococcus toxin have been well described by De Navasquez (1938), and we are not concerned with them in detail here. Knowing that this toxin produced sequestration of the renal cortex, we took advantage of this fact to demonstrate, if possible, a permanent diversion of blood through the medullary pathway. We were able to show this diversion even more successfully than we had hoped, and thus to demonstrate once again that when the blood is diverted from the renal cortex, the pathway traversed by the circulating blood is formed by the vessels associated with the juxtamedullary glomeruli Similar observations were made on the rat, though in this animal the technical difficulties of demonstrating the diversion of the blood flow from the cortex to the medulla proved to be greater.

The observations which have been described in this chapter were made in the light of the knowledge which we had acquired at this stage in our investigations of the changes which might occur in the intrarenal circulation. Many of the angiographs used in this study were from experiments which had been performed previously to determine the behaviour of the renal artery and renal vein under various conditions. In these angiographs and in others from a new series of experiments, most of which were made in the intact animal, we were able to see alterations in the normal cortical and medullary circulations, to an extent which varied considerably but which in some cases resulted in either an almost exclusively cortical circulation or in an almost exclusively medullary circulation. Indeed, in the experiments in which staphylococcus toxin was used, a permanent, exclusively medullary circulation was seen, an example of an extreme degree of change in the intrarenal circulation. These functional observations, combined with those described in Chapters I to III and with our morphological studies described in Chapter IV, have provided us with the basis for a new concept of the renal circulation. A brief recapitulation of our various findings and a presentation of this concept will be given in Chapter VI.

CHAPTER VI

A Survey of the Findings Described in the Previous Chapters

In the account of our experimental studies on the renal circulation which has been given in the preceding chapters, our observations have been presented in a more or less chronological order In each chapter we have indicated the problems which we tried to solve, the methods which we used in an attempt to solve them, and the results which we obtained from the experiments.

In this chapter we shall try to summarise our various findings, integrating them as far as possible and emphasising those observations which, in our view, may be of special significance in problems related to the function of the kidney We trust that the repetition which this survey must necessarily involve will not be tedious to the reader In addition, we shall make a few tentative suggestions in regard to the formation of urine, but we must stress the fact that these suggestions are not based on direct evidence, but are merely deductions from our own studies of the circulation and of the morphology of the kidney.

The original purpose of our investigation was to determine whether the changes found in the kidneys of patients dying of renal failure after crushing injuries of the limbs were due in any part to a vascular disturbance caused by reflexes initiated in the injured limb.

In our earlier studies, carried out in the rabbit, we found that prolonged constriction of one of the hind limbs produced by the application of a tourniquet resulted in widespread vascular changes, which made their appearance while the tourniquet was in position and continued to be present for a considerable time after its removal The most striking change was the marked constriction of the arteries supplying the hind limbs and of those supplying the kidneys; by contrast, the lack of any change in the artery supplying the intestines was most noticeable That [illegible] and renal arter[illegible] pressure was sh[illegible] calibres of these vessels might be wholly unrelated to a raised or lowered blood pressure Moreover, we found that vascular changes closely resembling those seen after the application of a tourniquet could be produced by stimulation either of the central end of the divided sciatic nerve or of the distal end of the divided splanchnic nerve, a finding which strongly suggested that the operation of some nervous reflex mechanism had contributed in no small

measure to produce the vascular changes seen after the *application of a tourniquet* Finally, we found that by dividing the splanchnic nerves before applying a tourniquet we were able to prevent the marked constriction of the renal artery which occurred in tourniquet animals with their splanchnic nerves intact. This finding was a further indication that the changes produced in the renal circulation of these latter animals had been caused *mainly or wholly* by the operation of a nervous mechanism.

From the results of these various groups of experiments, and in the absence of any evidence to the contrary, we concluded firstly that the prolonged constriction of a hind limb caused a substantial decrease in the volume of blood reaching the kidney, and secondly, *that this decrease in the renal blood* supply was due, in considerable part at least, to the operation of a reflex neurovascular mechanism, brought into play by impulses arising from the injured limb. But the vascular disturbance seen in these experiments was not limited to a decrease in the volume of blood reaching the kidney, for we *found that within the kidney itself the distribution of the blood might be profoundly altered.*

Realising at once the importance of this finding to renal physiology and pathology, we decided to suspend for the time being the general neurovascular studies and to direct our attention almost exclusively to a detailed investiga*tion of the intrarenal circulation and its pathways.*

Our angiographic studies of the intact animal had given us the first indication of the existence of a by-passing mechanism,[1] and from direct observations of the exposed kidney under various experimental conditions we had learnt that the blood flow might be diverted from the cortex and make its intra*renal circuit through a medullary pathway. As a result of these latter studies* it was also possible to state in general terms the region in which the by-passing channels were located; namely, the deepest zone of the cortex and the subcortical zone of the medulla. It was obviously of importance, however, to determine in detail the actual channels which formed the by-pass, for, as *Claude Bernard (1937) pointed out, anatomy localises physiology.* In the next stages of our work, therefore, we made a comprehensive investigation of the intrarenal vascular pattern and obtained more precise information about the routes taken by the blood under various conditions. As a result of this anatomical investigation and of further functional studies, our concept of the *variability of the intrarenal circulation* gained in precision on the structural side and in range on the functional one.

Throughout the research our studies have been of a very varied nature. On the functional side alone, three hundred animals have been used. *In* these experiments we have not attempted to determine all the effects of

... namely, the unexpectedly rapid appearance
the arterio-

many of the procedures used, but we have considered closely only those effects which appeared to us to have a special bearing on our immediate problem. In some instances these effects may have been relatively slight and, occasionally, they may have been unsupported by further experiments, but each observation has served to complement the information derived from other sources. On the anatomical side, we have used many methods in a study of the intrarenal vascular pattern, examining a wide range of material including not only the kidneys of our experimental animals, but also many human kidneys, both normal and pathological, and in addition the kidneys of various other mammals.

Thus, the concept we have formed of the renal circulation is based on a wealth of data derived from many and varied investigations: from angiographic studies of the intact animal and from direct observations of the exposed organs, both in normal animals and in those subjected to various forms of stimulation and to other experimental procedures, from the detailed examination of the vascular pattern in the kidneys of various mammals including man, and finally from the study of pathological kidneys both human and animal

It has already been pointed out that one of the most remarkable features of the redistribution of the blood within the kidney, seen in a number of our experimental animals, was the diversion of the blood flow from the cortex through a medullary pathway. We were surprised by this finding since we had not envisaged the possibility that a circulation might be maintained through the kidney by a route other than that which, it is commonly believed, invariably carries the renal blood flow, namely, the cortical route. As our studies progressed, however, we found ample evidence that the circulation through the cortex could be either diminished or even, in some circumstances, totally arrested *while a circulation continued through the medulla.*

We were able to demonstrate diversion of the intrarenal blood flow from the cortex to the medulla in the intact animal by means of angiographs This diversion of the blood flow and the varying degrees of cortical ischaemia resulting from it were indicated in the angiographs by a decrease of variable degree in the density of the cortical shadow and by a corresponding increase in the shadow of the medulla (see Chapter V) Further evidence that the cortex can become ischaemic whilst a circulation through the kidney is maintained was provided by visual observations of the exposed kidney (see Chapter III). The cortical ischaemia produced in these experiments was indicated by the blanching of the surface of the kidney, a blanching which was found to involve not merely the most superficial layer, but by far the greater part of the renal cortex While in some cases in which an extreme cortical pallor was produced there was undoubtedly a temporary cessation

of all renal circulation, there was clear evidence in many cases that some circulation through the kidney was being maintained during the period of cortical pallor. This evidence was provided by the fact that the blood continued to flow through the renal vein. The further observations that *during the period of cortical pallor* a stream of intensely red blood might appear in the renal vein or that the whole of the blood flowing through this vein might become arterial in colour, and that in either case the red blood might have a pulsatile flow, showed that a rapid circulation was in these cases continuing through the deeper parts of the kidney.

The exclusion of the renal cortex from the circulation and the maintenance of a blood flow through the medulla were further demonstrated in a convincing manner in animals in which an intravascular injection mass was introduced at the appropriate time. For, in many of these cases, in spite of the marked general constriction of the renal arterial tree which sometimes resulted from the experimental procedures used, the continuance of a circulation through the deeper parts of the kidney was shown by the appearance of the injected substance in the renal vein, although the surface of the kidney was unstained. The failure of the injected substance to circulate through the cortex in these cases and the striking filling of the medulla were well seen, both macroscopically and microscopically, when the kidneys were sectioned (see Figures 18, 19, 23, 24) These features were in marked contrast to the distribution of an injection mass in the normal animal (see Figure 22). The altered distribution was also well demonstrated radiographically in cases where a radiopaque substance was used (see Figures 21, 71).

It will be realised, therefore, that the diversion of the intrarenal blood flow from the cortex to the medulla, with a consequent cortical ischaemia of varying degree, has been studied and recorded by the use of a number of different methods The experimental procedures which resulted in the appearance of a cortical ischaemia were also many and varied. They included the application of a tourniquet to a hind limb; the stimulation of various nerves, in particular the central end of the divided sciatic nerve, the distal end of the divided splanchnic nerve, and the nervous plexus surrounding the renal artery; severe, rapid haemorrhage; and the administration of certain drugs, including adrenaline, pituitrin, and pitressin, in high dosages. In addition, some of our most remarkable examples of a diversion of the intrarenal blood flow from the cortex to the medulla were obtained after an injection of staphylococcus toxin. In susceptible animals, within twenty-four hours of the injection of the toxin, the peripheral, and indeed by far the greater, part of the renal cortex had become necrotic as a result of the diversion. In the same animals, in marked contrast to the conditions in the cortex, the circulation through the medulla was continuing and this region of the kidney was living and healthy (see Figures 67, 70).

In the case of experiments in which any of the procedures mentioned above were used, we attributed the diversion of the cortical blood flow to vasoconstriction in the peripheral parts of the cortex Our results indicate that the arterial vessels which are situated in the peripheral two-thirds (or thereabouts) of the cortical zone are more sensitive to stimuli than are those parts of the arterial tree situated proximal to these in the deepest layer of the cortex. For, as a result of various experimental procedures, we have seen peripheral segments of the interlobular arteries to be markedly constricted and sometimes even completely closed, while the proximal segments were relatively unaffected and so allowed the blood, which was barred from access to the peripheral cortex, to make an intrarenal circuit through the medullary pathway (Figure 71*b*).

It is clear, however, that the intrarenal blood flow can in some cases be diverted from the cortex by a means other than a vasoconstriction in the peripheral cortex We have seen such diversion to occur as a result of a dilatation of the vessels associated with the juxtamedullary glomeruli, caused by inhalation of amyl nitrite in large amounts (see Figure 29). We have also seen diversion to occur as a result of the blockage of the cortical glomeruli which takes place when thorotrast has been injected in large quantities (see Figure 31)

In contrast to the diversion of the intrarenal blood flow from cortex to medulla, described above, our experiments have shown some examples of an apparent diversion of this blood flow from medulla to cortex In these cases [illegible]

whose splanchnic nerves had been divided and which were then traumatised by the application of a tourniquet to a hind limb. In the angiographs of these animals we saw a remarkable increase in the shadow of the cortex, with an equally remarkable decrease in the shadow of the medulla (see Chapter V) The kidneys of these animals were injected with a mass at the conclusion of the experiment and on section revealed a most unusually complete filling of the cortex.

Although we have been able to record many examples of these changes in the distribution of the intrarenal circulation, and in particular a diversion of the blood flow from the cortex to the medulla, it must be pointed out that an experiment which in one animal had resulted in diversion of blood from cortex to medulla, when exactly repeated in another animal, not infrequently failed to produce a similar diversion. This variability in the reaction of the kidney in different animals of the same species was a striking feature in our experiments and its significance will be discussed in Chapter VII.

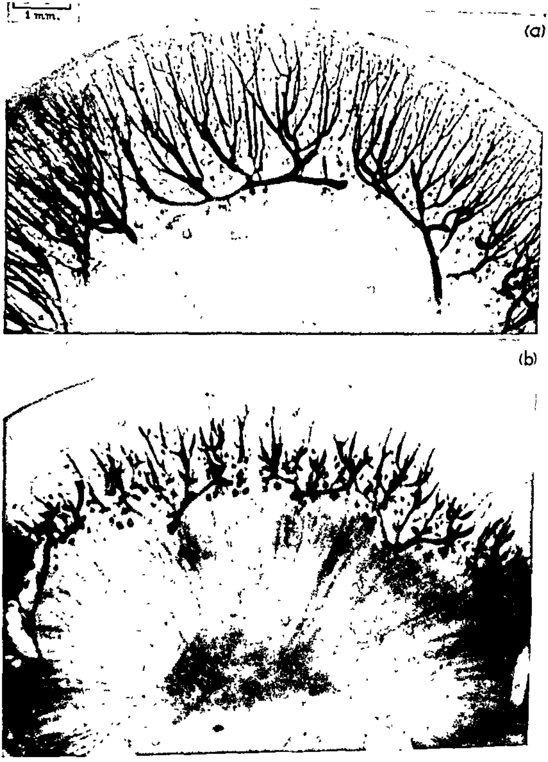


Fig. 71.

In general, however, despite the variations in the responses of different animals, we were impressed by the special sensitivity of the renal circulation. Our angiographic studies showed that, if a given experimental procedure resulted in any vascular changes, the renal artery was always involved although the arteries supplying the other abdominal organs might be unaffected. Moreover, the parallel responses of the arteries which supply the kidney and the hind limb respectively (the behaviour of the artery supplying the fore limb has not yet been adequately studied) suggest that anything which causes a disturbance of the circulation through the hind limb causes a similar disturbance of the circulation through the kidney. Further, within the kidney itself it appears that the vessels in the peripheral parts of the cortex are particularly sensitive to stimuli.

In addition, however, to the peculiar sensitivity of the artery which supplies the kidney and to the particularly ready response to stimuli shown by the smaller arteries which supply the more peripheral parts of the cortex, the renal circulation, and more especially the cortical circulation, shows a remarkable lability. In our studies of the exposed organ we saw not only that the surface of the kidney might become intensely pale as a result of appropriate experimental procedures, but also that it might show minor degrees of blanching and flushing even when no such procedures had been used. For these studies of colour changes in the surface of the kidney we were undoubtedly fortunate in that we were using rabbits and rats as our experimental animals. Had we been using cats or dogs, for example, we should have been less able to appreciate changes in the cortical circulation by means of visual observation, since in these species the large superficial veins of the kidney cover so much of its surface (see Figure 81). The continual slight fluctuations in the colour of the blood in the renal vein, which were seen in animals submitted to no experimental procedures other than that of anaes-

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FIG. 71. Radiomicrographs of sections of right and left kidneys of a rabbit, showing effect of faradic stimulation of nervous plexus surrounding the left renal artery. Colloidal bismuth had been injected during life via the aorta. (Both sections at same magnification.)

(*a*) Section of right (unstimulated) kidney. Contrast medium is seen filling the interlobular arteries to their terminations and also great numbers of cortical glomeruli. A few juxtamedullary glomeruli are seen, but the vasa recta are very poorly filled.

(*b*) Section of left [illegible]

me[illegible]

pr[illegible]

va[illegible]

ge[illegible]

medulla relatively dark (hyperaemic). Compare this difference with the much more uniform general density of these two regions in the section of the unstimulated kidney seen in (*a*).

The large vessels showing white in both (*a*) and (*b*) are empty veins, whose contents (contrast medium or blood) fell out when the sections were cut.

It is of interest to compare these radiomicrographs with those seen in Figure 67 *c* and *d*, which illustrate a diversion of the intrarenal blood flow from the cortex through the medullary by-pass caused by an intravenous injection of staphylococcus toxin.

thesia and laparotomy, were a further indication of the lability of the renal circulation.

Our studies have thus shown that the intrarenal blood flow does not in all circumstances follow a constant, invariable, and single course through the kidney, as hitherto commonly believed. Instead, the blood may circulate to a variable extent through the two main pathways which are present in the kidney, namely, the cortical and the medullary. Our evidence suggests that in ordinary circumstances the greater part of the intrarenal blood flow passes through the cortex and that only a smaller part circulates through the medulla. This habitually greater circulation through the cortical pathway in normal conditions, and the fact that the majority of the important functional elements of the kidney are situated in the cortex, together make any diversion of the circulating blood away from this part of the kidney of profound significance, especially when one considers the morphological arrangements of the structures associated with the cortical and medullary pathways respectively.

The vessels which form the channels of the medullary pathway are those associated with the juxtamedullary glomeruli; those which form the channels of the cortical pathway are the vessels associated with the cortical glomeruli (see Chapter IV) The difference in the morphological arrangement of the vessels which make up the two pathways comprises two striking features:

1. A marked disparity in size between the efferent vessels of the cortical glomeruli and the efferent vessels of the juxtamedullary glomeruli (Figure 72; see also Figures 44 to 47).
2. An equally marked disparity, both in size and arrangement, between the respective vascular beds into which the efferent vessels of the cortical and juxtamedullary glomeruli empty.

The vessels forming the cortical and medullary pathways respectively have been described by many workers since the time of Bowman (1842), but the dissimilarity between the vessels of the two pathways has not been stressed and the possibility that this dissimilarity is associated with a functional difference appears to have been overlooked. This lack of interest in the functional implications of differences in anatomical arrangement is perhaps not surprising since the structures have usually been studied from a purely morphological rather than from a physiological aspect. Our own studies of the intrarenal vessels were from the outset influenced by the unmistakable evidence, provided by our early experiments, that as a result of various traumatic experimental procedures changes might occur in the circulation of the kidney, and in particular in the relative distribution of the blood flow between cortex and medulla. Thus, the different pattern of the vessels making

up the cortical and medullary pathways assumed in our eyes a new significance in regard to their function.

The contrast in anatomical arrangement between the structures related to the cortical and medullary circulations respectively is not, however, confined to the channels which form the vascular pathways through these two regions of the kidney. A similar contrast is seen in the morphology of the respective nephrons which are associated with the blood vessels forming the cortical and medullary pathways, and in particular with the cortical and juxtamedullary glomeruli. As Peter (1909) showed, the most obvious difference is in the position and relative proportions of the various parts of the tubule, especially in the position of the loops of Henle and in the relative lengths of the thin segments of these loops (see Figure 54*a*). The loops of Henle of the tubules arising from cortical glomeruli pass only a relatively short distance into the medulla, and the thin segment of these loops is very short. On the other hand, the loops of Henle of the tubules of juxtamedullary glomeruli descend deeply into the medulla, often extending as far as the medullary papilla, and the greater part of each one of these loops is made up by the thin segment Notwithstanding these differences, there is one feature common to the loops of Henle of both types of nephron, namely, the fact that part of the loop of Henle lies in the medulla It must surely be of no small significance that considerable parts of all loops of Henle, including in every case the thin segment of the loop, are supplied by blood circulating through the medullary pathway.

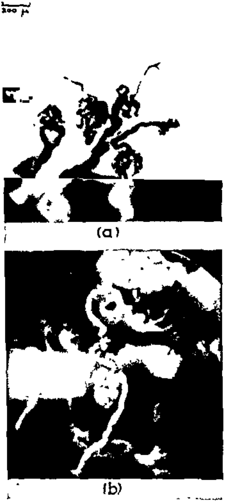

FIG 72 Neoprene casts from a normal human kidney (*a*) cortical glomeruli Note the very small calibre of the efferent vessels, as compared with the large calibre of the afferent arterioles (*b*) Juxtamedullary glomerulus Note that the efferent vessel (below) is of the same calibre as the afferent arteriole (above) The afferent arteriole of this glomerulus springs from an interlobular artery (partly seen at the top of the field), which is a branch of the 'arcuate' artery seen crossing the field transversely behind the glomerulus (Both photomicrographs at same magnification)

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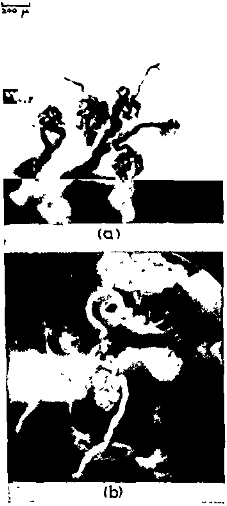

FIG 72 Neoprene casts from a normal human kidney (*a*) cortical glomeruli. Note the very small calibre of the efferent vessels, as compared with the large calibre of the afferent arterioles (*b*) Juxtamedullary glomerulus Note that the efferent vessel (*below*) is of the same calibre as the afferent arteriole (above) The afferent arteriole of this glomerulus springs from an interlobular artery (partly seen at the top of the field), which is a branch of the 'arcuate' artery seen crossing the field transversely behind the glomerulus (Both photomicrographs at same magnification)

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Such a suggestion is not entirely without support It is a generally accepted view that water is reabsorbed into the blood from the loops of Henle. A large number of vasa recta are adjacent to the loops of Henle where these lie in the medulla, and the walls of these vessels are morphologically well suited for the transference of fluid since they are composed of flattened endothelial cells. The vessels of the vasa recta system are most profuse in number and largest in calibre in the subcortical zone of the medulla, and in this region the *venous* elements of the system are strikingly predominant. This has been shown not only in our injected preparations (see, for example, Figures 42, 57), but also in angiographic studies of the living animal, in which the zone throws a heavy shadow in the early venous stage of the intrarenal circuit of the contrast medium (Figures 6*b*, 63*c*). In this zone, Peter's outer zone (see Figure 54*a*), are found the greatest number of loops of Henle seen at any level in the medulla, for it contains loops of Henle arising from both cortical and juxtamedullary glomeruli In this zone also are found the thin segments of the loops of Henle of all the cortical nephrons, as well as portions of the thin segments of the loops of Henle of all the nephrons of juxtamedullary glomeruli. Deeper in the medulla, in Peter's inner zone, the vasa recta are fewer in number but they are adjacent to the loops of Henle of the nephrons arising from the juxtamedullary glomeruli which at this level are composed of thin segments alone

In the thin segment of the loop of Henle the epithelium of the tubule is of flattened type and thus cannot be considered to be secretory It can be inferred, therefore, that any transference of fluid which takes place in this segment of the tubule is of a passive nature. The proximity of vasa recta, with their thin walls, to the thin segments of all loops of Henle would make possible the reabsorption of water from these segments of the tubules into the blood under the influence of either osmotic or hydrostatic pressure or a combination of both The striking profusion of the venous components of the vasa recta system in the zone where the loops of Henle, including thin segments of these loops, are most numerous, is in itself suggestive that the vasa recta are concerned with the reabsorption of water which takes place in this part of the tubule

Burgess, Harvey, and Marshall (1933) point out that pituitary extract (pitressin) has an antidiuretic action in birds and mammals, but not in amphibians or fishes. Since the evolution of the thin segment of the loop of Henle is the only new development in avian and mammalian kidneys that is not present in the kidneys of these lower vertebrates, they localise the site of the antidiuretic pituitary action to this segment of the renal tubule They believe the antidiuretic effect of pitressin to be due to a stimulation of water reabsorption by the thin segment, and in some cases also to a decrease in the volume of glomerular filtrate But, as we have just indicated, the cells forming

the vascular and the tubular structures associated with the cortical and medullary circulations respectively suggested the possibility that there were equally profound differences in their functions Having found that the cortex can be virtually excluded from the intrarenal circulation whilst the medullary pathway carries the diverted blood flow, we were led to speculate in particular on the functions of the vasa recta, the vessels which constitute by far the greater part of the medullary vascular bed.

The only function so far proved for these vessels is that which we ourselves have demonstrated, namely, that they act as channels for a variable amount of the intrarenal blood flow when this is diverted from the cortex. They may carry a lesser or greater proportion, or at times even the whole of the blood flow, according to whether the cortex receives a full normal supply, a reduced supply, or at times no blood at all. Our observations on the anaesthetised animal, subjected or not to various further procedures, do not lead us to believe that any large diversion of the blood away from the cortex occurs at all frequently in the quiescent unconscious state; indeed, we must admit that it is relatively difficult to provoke a complete reflex cortical ischaemia What may happen in the normal intact animal, leading its fully active life, may be different, and it is possible that under such circumstances major reflex or hormonal effects upon the circulation of the kidney are of fairly frequent occurrence. In any case, however, the adaptability of the vasa recta to variations in the amount of the intrarenal blood flow which they transmit may be but one aspect of their physiological importance, and we can legitimately inquire if any other functions have been, or can be, suggested for these channels.

The function of the vasa recta is generally considered to be a nutritional one, but the vasa recta themselves do not constitute a close-meshed capillary network such as one has learned to associate with nutritional functions elsewhere in the body. It is true that they resemble capillaries in the structure of their walls, but beyond this the similarity ceases and their only possible connection with nutrition lies in the fact that a capillary network is produced by offshoots from the efferent vessels of juxtamedullary glomeruli, in association with offshoots from the more proximal parts of the vasa recta. These very localised contributions, however, are subsidiary to the main picture of the medullary vascular arrangements and we are, on all counts, reluctant to regard the parent vessels as having any important nutritional role.

If then, as we believe, the vasa recta are not primarily nutritional vessels, and if they serve as the main conducting channels for the intrarenal blood flow only when it is diverted from the cortex, what is their function when the cortex is itself carrying the greater part of the blood flow? Is it possible that the vasa recta are concerned with the reabsorption of water and that this constitutes part of their function?

Such a suggestion is not entirely without support. It is a generally accepted view that water is reabsorbed into the blood from the loops of Henle. A large number of vasa recta are adjacent to the loops of Henle where these lie in the medulla, and the walls of these vessels are morphologically well suited for the transference of fluid since they are composed of flattened endothelial cells. The vessels of the vasa recta system are most profuse in number and largest in calibre in the subcortical zone of the medulla, and in this region the *venous* elements of the system are strikingly predominant. This has been shown not only in our injected preparations (see, for example, Figures 42, 57), but also in angiographic studies of the living animal, in which the zone throws a heavy shadow in the early venous stage of the intrarenal circuit of the contrast medium (Figures 6*b*, 63*c*). In this zone, Peter's outer zone (see Figure 54*a*), are found the greatest number of loops of Henle seen at any level in the medulla, for it contains loops of Henle arising from both cortical and juxtamedullary glomeruli In this zone also are found the thin segments of the loops of Henle of all the cortical nephrons, as well as portions of the thin segments of the loops of Henle of all the nephrons of juxtamedullary glomeruli. Deeper in the medulla, in Peter's inner zone, the vasa recta are fewer in number but they are adjacent to the loops of Henle of the nephrons arising from the juxtamedullary glomeruli which at this level are composed of thin segments alone

In the thin segment of the loop of Henle the epithelium of the tubule is of flattened type and thus cannot be considered to be secretory. It can be inferred, therefore, that any transference of fluid which takes place in this segment of the tubule is of a passive nature The proximity of vasa recta, with their thin walls, to the thin segments of all loops of Henle would make possible the reabsorption of water from these segments of the tubules into the blood under the influence of either osmotic or hydrostatic pressure or a combination of both The striking profusion of the venous components of the vasa recta system in the zone where the loops of Henle, including thin segments of these loops, are most numerous, is in itself suggestive that the vasa recta are concerned with the reabsorption of water which takes place in this part of the tubule

Burgess, Harvey, and Marshall (1933) point out that pituitary extract (pitressin) has an antidiuretic action in birds and mammals, but not in amphibians or fishes Since the evolution of the thin segment of the loop of Henle is the only new development in avian and mammalian kidneys that is not present in the kidneys of these lower vertebrates, they localise the site of the antidiuretic pituitary action to this segment of the renal tubule They believe the antidiuretic effect of pitressin to be due to a stimulation of water reabsorption by the thin segment, and in some cases also to a decrease in the volume of glomerular filtrate. But, as we have just indicated, the cells forming

the walls of the thin segment of the loop of Henle are not of secretory type. We suggest, therefore, that the antidiuretic effect may be partly due to an increase in *passive* reabsorption of water into the blood in the vasa recta through the thin walls of this segment, resulting from a readjustment in the distribution of the intrarenal blood flow between cortex and medulla.

In putting forward this suggestion we do not ignore the fact that the thick segments of the loops of Henle and the convoluted tubules, with their cells of secretory type, also play their part in the reabsorption of water. But the close relationship between the thin segments of *all* loops of Henle with the large vessels of the medulla, namely, the vasa recta, suggests that these thin segments play a particularly important part in the reabsorption of water. Any variations in the blood flow through the cortex must affect glomerular filtration But, as we have demonstrated, such variations in the blood flow through the cortex are reflected in the blood flow through the medulla, which appears to be inversely proportional to the cortical flow. It seems reasonable to expect that variations in the circulation through the medulla will affect the reabsorption of water in this region, whether this be active or passive. We have given above our reasons for suggesting that it is partly passive.

A possible objection to our hypothesis may be raised because of the peculiar arrangement of the vasa recta. Admittedly, the vasa recta lie in close-set bundles and some of the individual vessels are contiguous with, and occasionally completely surrounded by, their fellows, a disposition which would appear to be unfavourable for reabsorption of fluid from the tubules. But thin segments of loops of Henle are found intermingled with the vasa recta in their bundles, and the vessels on the periphery of each bundle are everywhere adjacent to thin or thick segments of the loops of Henle. Moreover, although at some levels an individual vessel may be completely surrounded by other vasa recta, at deeper levels, as more and more vasa recta turn back towards the cortex, this vessel will probably come to be adjacent to a segment of tubule, and thus at this site be in a position to permit direct reabsorption of water. In any case, it may well be that the interstitial fluids play a part in effecting a transference of fluid between the tubules and the vasa recta.

In connection with the above observations in regard to the relation of the vasa recta to water reabsorption, it may be of interest to record briefly the information which our studies have provided in regard to the rate of blood flow through the vasa recta as compared with that through the cortical vessels The vasa recta make up by far the greater part of the vascular bed which constitutes the medullary pathway, and our observations suggest that normally, when the cortex is in full activity and the medullary pathway is carrying only the smaller proportion of the total intrarenal blood flow, the circulation through this pathway is appreciably slower than that through the cortical pathway For our angiographs of normal rabbits have shown that the shadow

of the contrast medium reaches the medulla later than the cortex, and also that it clears from the medulla more slowly than it clears from the cortex. Moreover, the morphology of the channels which form the medullary pathway in itself suggests that the rate of flow through these channels is normally slower than the rate of flow through the cortical vessels. As we have already shown, the efferent vessel of the juxtamedullary glomerulus is much larger in calibre than the efferent vessel of the cortical glomerulus, and the rate of flow [illegible]

In the succeeding stage of the medullary pathway the rate of flow must be greatly reduced since the efferent vessel of the juxtamedullary glomerulus divides into a number of vasa recta, each of which is of virtually the same calibre as its parent trunk The flow must become still slower as the blood approaches the venous end of the vasa recta, where the vessels are of even larger calibre and considerably more numerous than they are on the 'arterial' side. Finally, since the vasa recta empty into vessels which drain in common both cortex and medulla, at times when these collecting veins are carrying the greater outflow from an active cortex the outflow from the vasa recta may well be impeded

While, however, the above suggestion as to the primary function of the vasa recta under basal conditions, when the cortex is carrying the greater part of the blood supply, cannot at present be considered as more than a hypothesis, we have evidence that when the blood supply to the cortex is reduced—a reduction which may be of variable degree and even so great as to result in a complete cortical ischaemia—these vessels play a special role In these circumstances the vasa recta serve primarily as conducting channels and carry through the medulla the blood flow which is diverted from the cortex At such times we believe that the circulation through the vasa recta is more rapid An accelerated flow through the medullary pathway has been indicated by various observations which have been described in previous chapters For instance, in angiographic records of tourniquet animals the contrast medium has been seen to appear in the renal vein at an earlier stage of its intrarenal circuit than in normal animals. The view that this quick passage of the contrast medium was made by way of the vasa recta is supported by the fact that in these cases the arterial angiograph, in which the contrast medium is already beginning to make its appearance in the renal vein, shows a shadow in the medulla whilst there is little if any shadow in the cortex, a picture the reverse of that seen in the arterial angiographs of normal animals. Presumptive evidence that in conditions of cortical ischaemia the flow through the vasa recta is accelerated was provided by the appearance in the renal vein of blood which was arterial in colour, at a time when the surface of the kidney was pallid. Evidence of a similar character was obtained from results

of injections of Indian ink, introduced into the renal circulation from the arterial side under similar experimental conditions. For the ink was seen to appear in the renal vein almost simultaneously with its appearance in the renal artery, the cortex, which was pallid at this stage, remaining unstained by the ink. The pulsatile flow of the arterial stream in the renal vein, which was sometimes seen in uninjected animals, was demonstrated very clearly in some of the animals injected with ink, and in which we saw jerky forward movements of discrete particles of black suspended in the red stream.

To these functional indications that in conditions of cortical ischaemia the rate of flow through the vasa recta is increased, one further remark may be added. With little or no blood circulating through the cortex, the amount of blood passing through the vasa recta must be increased, although the total renal inflow may be diminished. This increase in the medullary circulation, and the fact that on leaving the medulla the blood has a more or less exclusive use of the vessels which drain in common both cortex and medulla, together suggest that in these circumstances the rate of flow through the vasa recta is increased.

In the discussion of our various studies in this chapter we have touched only on the fringe of the theoretical implications arising from the work, and we hope that many of the problems raised will be investigated by other workers who have the necessary facilities for the specialised investigations involved. Our object in publishing now the results which we have so far obtained has been to make available for other workers findings which, we hope, will stimulate a renewed attack on the unsolved problems of renal physiology and pathology. For our researches have shown that all questions relating to the kidney and its function should be reviewed in a new light, since this organ has a duality in its circulation which has hitherto been unsuspected. In fact, we venture to put forward a new concept of the circulation through the kidney and thus, inevitably, of the kidney itself. This concept may be summarised as follows:

> **The course taken by the blood in its passage through the kidney does not show *that degree of constancy which has commonly* been imagined. In fact, the kidney has two potential circulations, a greater and a lesser, and in extreme conditions the blood may pass either almost exclusively through one or other of two pathways, or, in less abnormal circumstances, to a varying degree through both. The vessels making up the pathway of the greater *circulation are* those associated with the cortical glomeruli; the channels of the lesser circulation are those associated with the juxtamedullary glomeruli.**

Our experimental work has been carried out on rabbits and rats, but the anatomical structures which provide a foundation for our concept are present

in all the mammalian kidneys, including the human, which we have examined. It is, therefore, reasonable to believe that the redistribution of the intrarenal blood flow seen under experimental conditions in our animals occurs also under certain conditions in the kidneys of other animals, including man.

This belief gains support from the findings of many workers who have attempted to reproduce in various experimental animals the physiological changes shown by, and the pathological conditions found in, the human kidney. Convincing evidence that comparable alterations in the distribution of the intrarenal blood flow occur in the human kidney is to be found in the results of the natural 'experiments' carried out by disease processes.[1] These various findings will be discussed in Chapter VII.

[1] 'Numberless pathological lesions . . . are real experiments, by which physicians and physiologists profit, without any purpose on their part to produce the lesions, which result from disease' (Claude Bernard, 1927, p. 10)

CHAPTER VII

Pathological and Clinical Implications of these Studies

In this chapter we shall discuss some of the physiological and pathological findings of other workers, and consider to what extent these findings support the views which we have put forward as a result of our own studies We shall also, with diffidence, try to assess some of the clinical implications of our observations.

As a result of our studies we have formed a new concept in regard to the renal circulation, which is essentially as follows:

The blood reaching the kidney has two potential routes through that organ and, according to circumstances, it may pass almost exclusively by one or other of these routes, or in varying proportions through each of them.

The two routes diverge where the afferent arterioles of the juxtamedullary glomeruli leave the interlobular arteries. One route, the medullary, continues through the juxtamedullary glomeruli, the efferent vessels of these glomeruli and their derivative vasa recta, to the interlobular veins. The other route, the cortical, continues through the interlobular arteries, the afferent arterioles of the remaining glomeruli, these glomeruli themselves, their efferent vessels and the cortical intertubular capillary network into which these break up, and finally through the veins draining this network into the interlobular veins. The rest of both routes, like their beginning, is identical and is through ever larger venous trunks to the main renal vein.

Thus, the renal circulation has a duality not previously ascribed to it, since the frequent fluctuations in the distribution of the intrarenal blood flow between the cortical and the medullary vascular pathways have hitherto not been appreciated

The fact that the glomerular circulation may be intermittent has been definitely established in the kidneys of amphibians (Richards and Schmidt, 1924), and we consider that this is a phenomenon comparable with a diversion of blood from the cortex such as we have described in mammals. In fact, though the morphological arrangements in the amphibian kidney are of course very different, the findings in amphibians described by Bieter (1935) are in many respects closely paralleled by our own observations on the kidneys of mammals, particularly in regard to nervous stimulation. White (1939), as a result of studies of injected kidneys of dogs and rabbits, came to the conclusion that under normal conditions glomerular intermittence did not occur in the mammalian kidney, but he did not exclude the possibility that

extreme conditions, such as severe haemorrhage or a sudden increase in the output of adrenaline, might induce such intermittence.

Our studies have shown that large numbers of glomeruli may in fact be excluded from the circulating blood[1] and that the [illegible] intermittence, as we have seen it in [illegible] vastly greater scale than that reporte[illegible] and Schmidt (1924) and Bieter (1935), and that sought by White (1939) in the kidneys of the dog and rabbit Smith (1943) undoubtedly envisages the possibility that glomeruli may cease to transmit the circulation; indeed, he states 'it is conceivable that blood can be shunted away from both glomerulus and tubule, rendering the entire nephron inactive'.

The possibility that the blood may be diverted from the cortex to make its intrarenal circuit through a medullary pathway has not hitherto been seriously considered in the theories which have been put forward in regard to the secretion of urine It is clear, however, that changes in the intrarenal circulation such as those we have described must have a profound effect on the function of the kidney, since this function depends first and foremost on the circulation through the organ. We appreciate the possible scale of the effects of a redistribution of intrarenal blood flow all the more when we remember the enormous volumes (of blood carried to glomeruli, fluid filtered, and fluid reabsorbed) involved in the formation of urine Smith (1943) estimates that in the human subject the blood flow passing through both kidneys amounts to 1,200 ml. per minute; that is, up to a quarter of the total output of the heart This would represent a blood flow of more than 1,700 litres in twenty-four hours.[2]

It is believed that approximately 10 per cent of the fluids of the blood circulating through the kidney are removed by glomerular filtration,[3] that is to say, on the basis of Smith's figures, 170 litres in twenty-four hours. The amount of urine, however, excreted over the same period is only about 1·5

[1] The diversion of the circulating blood from the superficial vascular bed of the kidney through a deep intra- [illegible]

[2] Dunn's (1940) estimate, which he considered to be a conservative one, was 1,080 litres in twenty-four hours

[3] Ekehorn (1931) is inclined to believe that 25 to 30 per cent of the fluids of the blood may be removed by glomerular filtration

litres, and consequently 168·5 litres of the glomerular filtrate must be reabsorbed. In no other organ of the body do such astonishingly large exchanges of fluids take place, and we have all the more reason for wonder when we remember that the total weight of both kidneys is of the order of only one quarter of a kilogram.

The tacit acceptance of the constancy of the course taken by the intrarenal blood flow probably accounts for the fact that, ever since the modern theory of renal function was introduced by Cushny (1917), many workers have paid more attention to reabsorption than to glomerular filtration as the factor predominantly concerned with variations in the output of urine. But glomerular filtration must be influenced by changes in blood flow and, as we have shown, some or even much of the blood flowing through the kidney may be diverted from the cortex through the medullary by-pass. It seems probable, therefore, that changes in the rate of glomerular filtration due to changes in cortical blood flow are as important a factor in causing variations in urine output as is the rate of tubular reabsorption, although the latter in its turn is probably influenced by the concomitant inverse changes in the medullary blood flow.

It is universally accepted that the energy required for glomerular filtration is provided by the blood pressure, and it is recognised that in order to overcome the osmotic pressure of the blood a definite glomerular pressure must be provided in order to maintain filtration. But if filtration is to be maintained,

glomerular loops, the volume of the blood within the glomerulus is reduced, the glomerular pressure therefore tends to fall, and the osmotic pressure to rise. Without replacement of fluid, the combination of these two processes would quickly lead to a cessation of filtration, while the packing of the red cells in the glomerular capillaries would impede any later resumption of blood flow (this packing with red cells is sometimes seen in certain pathological conditions). If filtration is to continue at a constant rate the blood must be continuously renewed by an adequate flow.

We are well aware that our experimental observations have been limited mainly to the renal circulation, but the changes in the distribution of the intrarenal blood flow which we have demonstrated must affect the function of the glomeruli, whatever other factors may be involved. It has been assumed that in the mammalian kidney *all* nephrons have identical functions. We should like, however, to suggest the possibility that the nephrons arising from the cortical and juxtamedullary glomeruli respectively do not have precisely the same functional activities. We have as yet no direct evidence on this point, but the striking differences in their morphology, in their situation in the kidney (Figure 54), and not least in their vascular environment,

would favour such a hypothesis. Studies such as those made by Walker and Oliver (1941), with their technique of tubular puncture, will perhaps eventually resolve this point.

We ourselves have undertaken no studies of renal function by the various methods which have been devised for this purpose, including the much used renal clearance tests. But, by a consideration of the findings of other workers who have used these methods, our concept gains support of a nature which we have not as yet been in a position to provide ourselves. In addition, it is perhaps possible that diversion of the blood flow from the cortex, such as we have seen in our experiments, may provide an explanation for some of the apparent inconsistencies which have been noted by various workers in the results of renal function tests and of studies of the renal blood flow

The literature on the kidney has become so vast that it would be impossible to attempt to review it here, even were we in a position to do so. We may say at once, however, that in no work with which we are familiar have results been reported which are incompatible with our own findings, or which vitiate our concept.

From the outset of our work we had a special interest in the causes of anuria, and especially of the anuria which may result from activities of the nervous system In this connection it is significant that O'Connor and Verney (1942, 1945) were able to inhibit water diuresis in the bitch by emotional stress The inhibition was of two types, rapid and slow, and they showed that the rapid inhibition occurred only when the nerve supply to the kidney was intact, and that the slow inhibition was due to the release of an antidiuretic substance from the posterior lobe of the pituitary body There seems every reason to believe that in the case of the rapid inhibition of water diuresis the effect was produced by diversion of part of the intrarenal blood flow from the cortex, such as we have seen to occur in our experimental animals as a result of nervous stimulation. A diversion of cortical blood flow produced by a nervous agency is, as we have found, caused by a vasoconstriction which is particularly marked in the arterial vessels situated in the peripheral parts of the cortex O'Connor and Verney themselves postulated that the rapid inhibition was due to constriction of the renal vessels It appears to us possible that the slow inhibition of water diuresis was also effected by a similar diversion of the cortical blood flow, since we have seen indications of such a diversion after injections of pituitrin or pitressin, although admittedly these hormones were given to our animals in high dosages. If this is a correct explanation of the slow inhibition of water diuresis in the dog, the same explanation might be given for the inhibition of water diuresis effected in man by nicotine, an inhibition which Burn, Truelove, and Burn (1945) attribute to stimulation of the posterior lobe of the pituitary body with a consequent discharge of its hormones

We suggest that variations in the distribution of intrarenal blood flow

may also account for many of the temporary disturbances of renal function and alterations in the calculated renal blood flow recorded in human subjects by Smith (1939–40, 1943) in conditions which included anxiety and changes in posture, and also after the injection of adrenaline and pyrogens. In our own experiments we found that direct nervous stimulation and the injection of adrenaline, as well as injections of posterior pituitary hormones, might produce a diversion of the blood flow from the cortex, and this fact lends support to our suggestion that a similar mechanism may have been operating in the cases reported by Smith In circumstances of anxiety, very similar to those that produced a disturbance of renal function in Smith's cases, Wolf and Wolff (1943) recorded a dramatic blanching of the mucosa of the stomach which occurred simultaneously with a marked pallor of the face. It would be interesting to know whether the surface of the kidney paled at this time, for our own observations suggest that the circulation of the kidney is more sensitive to stimuli than is the circulation of other abdominal viscera.

It is well known that the sympathetic nervous system exercises a greater effect on vascular tone when the erect posture is assumed. In this posture the output of urine is not as great as it is in the recumbent position (Brun, Knudsen, and Raaschou, 1945), in spite of a rise of blood pressure. Since, as we have shown, the peripheral parts of the renal arterial tree constrict more readily than the proximal parts, we envisage the possibility that the slightly reduced output of urine which occurs in the erect posture may be due to a minor diversion of the blood flow from the cortex.

In addition to the examples mentioned above, we believe that our findings may provide an explanation for the normal variations in the output of urine under many conditions of daily life; for instance, the changes in output due to changes in temperature, including the much reduced output of urine in great heat, the reduction in output during muscular exercise, and that following reduced fluid intake or, conversely, the increased output which follows the drinking of much fluid. The difference in nocturnal and diurnal urinary secretion may perhaps also be explained by a difference in the distribution of the intrarenal blood flow.

It may well be, moreover, that diversion of the intrarenal blood flow from cortex to medulla accounts for some of the apparent anomalies and inconsistencies in the results obtained in tests of renal function reported by some workers For example, Selkurt (1946, *b*) carried out a series of experiments [illegible] renal blood [illegible] is [illegible] method, and simultaneously made clearance tests of [illegible] to hippuric acid (PAH) on the samples of blood thus obtained. He found that during the periods of hypotension following the bleeding there was anuria and clearances were zero even whilst appreciable amounts of blood were flow-

ing through the kidney. In the same animals, on re-infusion of the blood, despite the restoration of the blood pressure to adequate levels, the clearances of PAH and creatinine failed to be restored, resulting in large disparities between the calculated blood flow based on PAH clearance and the renal blood flow measured directly. He considered that, at this stage, the clearance of creatinine no longer measured filtration rate, for it remained reduced to a far greater extent than could be expected with the existing conditions of blood pressure and renal blood flow. The discrepancy between the directly measured renal blood flow and the calculated renal blood flow was of the order of 60 per cent or more In the light of our own findings we suggest that this apparently anomalous result was due to diversion of the intrarenal blood flow from the cortex to the medullary pathway. Such a diversion and a consequent increase in the circulation through the medullary channels would account for the fact that the renal blood flow, recorded by direct measurement, was considerable, while at the same time the rate of glomerular filtration, as calculated by clearance tests, was markedly reduced Our studies in the rabbit have shown that after severe, rapid haemorrhage the blood flow passing through the cortex may be noticeably reduced while the circulation through the medulla shows a corresponding increase (see Figure 66*a*). In another series of experiments in dogs, Selkurt (1946, *a*) noted similar disparities between renal blood flow as calculated by clearance tests and that determined by direct measurement These observations were made after release of a clamp which had occluded the renal artery for a period of twenty minutes. Selkurt concluded that one factor contributing to the disparity in the measurements might be a reduction in glomerular filtration pressure, caused by arteriolar vasoconstriction following the period of ischaemia To this conclusion we would add the suggestion that the vasoconstriction was more severe in the most peripheral parts of the cortex than elsewhere, for if, as a result of such a vasoconstriction, blood was being diverted from the cortex through the medullary pathway, this would explain why the renal blood flow as calculated by clearance tests was noticeably less than the directly measured renal blood flow

In connection with Selkurt's findings, the result of another of our experiments, which was described in Chapter III, may be recalled. In this experiment an intravenous injection of adrenaline in high dosage caused a temporary cessation of the circulation through the kidney. We saw, however, that when this circulation was resumed, the course taken by the blood in its intrarenal circuit was mainly that of the medullary pathway (see Figure 20).

Lauson, Bradley, and Cournand (1944), using clearance methods in a study of shock in human subjects, found that the proportion of the cardiac output which circulated through the kidneys was considerably less than normal, indicating that renal vasoconstriction shunted blood away from the functional

tissues of the kidneys to other parts of the body. They were conscious of the limitations of clearance methods when applied to cases of shock and of the need for caution in the interpretation of their results, but they stressed that the decrease in the renal circulation resulting from shock was very great, all possible errors notwithstanding. They found that glomerular filtration was reduced far more than could be accounted for by the reduced arterial pressure, but they also found considerable variations in different patients. For example, glomerular filtration rates between 10 and 20 ml. per minute were associated with mean arterial pressures ranging from 50 to 100 mm. Hg. Conversely, a mean arterial pressure of 70 mm. Hg. was associated in one case with a filtration rate of only 3 ml. per minute and with a rate of 120 ml. per minute in another. Our own findings in haemorrhagic shock suggest that the disproportion between the decrease in glomerular filtration and the fall in blood pressure, observed in these human cases, was due to the fact that part of the intrarenal blood flow was being diverted from the cortex through the medullary by-pass Differences in the extent of diversion in different individuals would account for the lack of correlation between filtration rates and the levels of mean arterial pressure. Lauson and his colleagues inclined to the view that the vasoconstriction did not affect the whole kidney uniformly, but that it resulted in a reduction of blood supply which was limited to some nephrons or possibly to some whole anatomical units of nephrons.

Corcoran and Page (1943), studying in dogs the effects of haemorrhage on renal function by means of clearance tests, also found that glomerular filtration was depressed disproportionately to the degree of hypotension produced. Because of the wide changes in renal blood flow and in excretion rate which might result from only slight changes in blood pressure, they thought it likely that during hypotension the renal blood flow was distributed unevenly through the renal vascular bed, being greatest in sites of least resistance. Our studies have suggested that these sites are found at the entrance to the medullary by-pass, in the juxtamedullary glomeruli, whose efferent vessels and the vasa recta into which they empty are very much larger in calibre than are the efferent vessels of the cortical glomeruli and the cortical intertubular capillaries into which these efferent vessels empty.

Van Slyke, Rhoads, Hiller, and Alving (1934) record a remarkable phenomenon which they observed in their studies on urea excretion in unanaesthetised dogs with explanted kidneys. They found that generally the renal venous blood contained between 6 and 12 per cent less urea than the renal arterial (in point of fact, jugular vein) blood, but on several occasions they noticed that for short periods the renal venous blood contained actually more (up to 27 per cent more) urea than was present in the renal arterial blood. This unexpected reabsorption of urea from the kidney by the blood was not due to cessation of renal blood flow, which appeared to be normal.

They could not determine the mechanism of the phenomenon, which they attributed to some reflex initiated by the slight trauma involved in the puncture of the renal vein. Since we have seen in our experiments that stimuli applied in the neighbourhood of the renal vessels may cause diversion of the intrarenal blood flow from the cortex to the medulla, we are tempted to

arterial blood it is difficult to understand, unless the diversion, by diminishing the cortical blood supply and thus causing a cortical anoxia, rendered the cells in the cortex which are normally engaged in concentrating urea incapable of continuing their metabolic activities, and consequently their contained urea diffused back into the reduced cortical blood flow. A possible explanation of the unexpected result of the estimation of oxygen tension in the renal venous blood, which Van Slyke and his colleagues obtained on these occasions, may be found in the fact that this blood, like the blood in many other veins, is not always homogeneous but may at times be composed of several distinct streams, in which the oxygen tension is presumably different since the colour of the blood in the individual streams may be totally different (see Chapter III for observations on streamlines) Thus, blood withdrawn by means of a needle inserted into the renal vein cannot necessarily be assumed to represent an average sample of the blood leaving the kidney since, depending on the exact position of the needle point, the sample may be drawn from a red or a blue stream. In many of our experiments we saw that diversion of the cortical blood flow was accompanied by the appearance of blood of arterial colour in the renal vein.

Addis and Shevky (1917), working with rabbits, had at an earlier date observed that, occasionally, blood withdrawn from the renal vein contained more urea than was present in the blood in the renal artery. At the times when this phenomenon occurred no urine was being secreted, a finding which they attributed to vasoconstriction resulting from the manipulations required for the removal of the renal venous blood. They believed that the increase in the urea content of the blood in the renal vein was due to the relaxation of a force which is normally operative, retaining a high concentration of urea within the kidney. It appears to us that the 'force' envisaged by Addis and

of the urea stored in the tubular cells in the cortex

A reflex diversion of part of the cortical blood flow would also explain the reduced urea extraction recorded by Dunn, Kay, and Sheehan (1931)

in some of the rabbits used in their experiments. They themselves attributed the interference with renal function in some of the animals in which a reduced urea extraction was recorded to the fact that they had in these cases squeezed out the bladder before the experiment.

As we have pointed out, changes in the distribution of the intrarenal blood flow between cortex and medulla must have a profound effect upon the formation of urine by effecting changes in glomerular filtration. But it seems probable that such changes in the distribution of the blood flow also have an effect on the reabsorption of water from the tubules and thus further influence the output of urine. Variations in the amount of blood supplying the secreting cells must clearly be accompanied by variations in the activities of these cells. In addition, however, we suggest that variations in the distribution of the intrarenal blood flow may result in variations in passive reabsorption of water from the thin segments of the loops of Henle. The close proximity of these thin segments to the thin-walled vessels of the vasa recta system, and especially to its venous components, suggests that passive transference of fluid from the thin segments of loops of Henle to the vasa recta may constitute an important part in the reabsorptive process. Moreover, is there not some significance in the fact that the vasa recta which lie adjacent to the thin segments of *all* the loops of Henle form by far the greater part of the pathway through which the blood is carried when it is diverted from the cortex?

The output of urine may be relatively constant when the body is at rest, but it seems probable that with the stresses and strains of active life, changes of posture, muscular exercise, changes of temperature, and, not least, emotional disturbances, there must be frequent fluctuations in the distribution of the intrarenal blood flow and consequent fluctuations in the formation of urine. We have been impressed by the extraordinary lability of the circulation through the renal cortex, even in our anaesthetised animals, and in a short series of experiments (the only ones which we have so far attempted with this object in view) we have correlated this lability of the blood flow with fluctuations in urinary output, as gauged by the passage of peristaltic waves down the ureter. So we believe that in general the two changes may often be associated. We have already referred to the profound influence of emotional stress on the secretion of urine, which has been demonstrated in dogs by O'Connor and Verney (1945) and reported by Smith (1939–40) in man. Smith (1939–40) does not believe that changes in renal function due to emotion are of frequent occurrence in man, but if O'Connor and Verney (1945) were able to produce such marked changes in diuresis in the dog by relatively minor emotional stimuli, it seems reasonable to expect that similar changes may occur frequently in man, with his more highly developed cerebral cortex and his greater capacity for emotion.

The direct part played by the autonomic nervous system in controlling renal function is frequently discounted at the present time, because it has been shown that animals can live and produce a normal urine with denervated kidneys, or even with kidneys transplanted to another site in the body. In actual fact, however, they can do this only so long as they remain in an artificial and protected environment, and the real point is not that they survive, but that they have to live under these artificial conditions if they are to survive, because the denervation has reduced their adaptability and in consequence their ability to withstand adverse conditions. So their range of activity has been lessened and they are no longer to be regarded as normal animals. Cannon (1932), for instance, removed the sympathetic nervous system from cats and found that they continued to live, but he pointed out that their life in the laboratory was a limited sort of existence, in which they were not exposed to marked changes of temperature, had no need to struggle for food or to escape from enemies, and ran no risk of haemorrhage The deficiencies of the sympathectomised animals were clearly shown when they were exposed to heat or cold We ourselves would add that such animals are at a particular disadvantage, as compared with normal subjects, in that they have lost the power, when occasion arises, of rapidly diverting their renal blood flow from the cortex through the medullary by-pass

We believe that the nervous system is an essential factor for the maintenance of a constant fluid balance in the body in all circumstances, and particularly under conditions of stress, and we believe, further, that it achieves this end by regulating the distribution of the blood flow between the two circulations of the kidney, the cortical and the medullary The regulation may be effected by direct nervous control or through the intermediation of liberated hormones or, more probably, by a combination of both these factors

The influence which the posterior pituitary hormone exercises on the output of urine is beyond dispute The effectiveness of subcutaneous injections of pitressin in reducing the copious flow of urine in diabetes insipidus is well known It is generally believed that the antidiuretic effect of the posterior pituitary hormone is the result of increased reabsorptive activity due to stimulation of the secretory cells of the tubules We consider, however, that another factor may also be involved, namely, that the pituitary hormone, by its direct action on the renal blood vessels, causes blood to be diverted from the cortex through the medullary by-pass, with a consequent decrease in glomerular filtration

It is of interest that it is only mammals which possess well developed loops of Henle with thin segments, and that these animals alone produce a hypertonic urine Moreover, the posterior pituitary hormone has an antidiuretic effect only in those kidneys in which there is a loop of Henle (see Chapter VI),

that is to say, in mammals which have a medullary circulation closely associated with these loops. If the effect of the antidiuretic hormone is to cause increased activity of the secretory cells of the tubule, as is commonly supposed, why does the hormone have no antidiuretic effect in species in which all the tubular cells which are found in mammals are present *except* for the cells of the thin segment of the loop of Henle? Further, if the secretory cells alone are responsible for reabsorption of water from the tubules, why do not patients develop a polyuria when their general cellular activity is depressed by a 'toxaemia', such as occurs in severe infections? On the basis of the theory that reabsorption is wholly an active cellular process, one would expect that in these circumstances reabsorption would be greatly diminished since, presumably, the activity of the cells of the tubules would be decreased in common with the activity of the cells elsewhere in the body, and consequently the flow of urine would be copious. The cloudy swelling seen in the tubular cells of such cases provides evidence that a severe metabolic disturbance has been present.

We do not discount the reabsorptive function of the convoluted tubules, but we believe that the loops of Henle, and particularly the thin limbs of these loops, play an important part in the regulation of the intrarenal fluid balance. The intimate relation of the thin limbs of these loops to the vessels of the medullary circulation, particularly those on the venous side, suggests that this circulation is an integral part of the mechanism by which the volume and tonicity of the urine are regulated On this assumption, we suggest that while a decrease in the cortical circulation, resulting from diversion of the blood flow from cortex to medulla, causes a diminution in glomerular filtration, the increase in the medullary circulation, which also results from this diversion, may simultaneously cause a greater reabsorption from the loops of Henle in the medulla We have seen that the blood may make a medullary circuit by routes of various lengths, since individual vasa recta turn back towards the cortex at all levels in the medulla, from the subcortical zone to the apex of the papilla (see Figures 38, 39, 50). It may well be that the length of the particular route taken by the blood in making its circuit through the medulla, that is to say, the depth in the medulla to which it passes, is a factor which influences the reabsorptive process.

We have suggested above that changes in the renal circulation, and in particular a variable distribution of the intrarenal blood flow between cortex and medulla, reflect the operation of a normal vascular mechanism for maintaining the fluid balance of the body. We have also suggested that these changes are effected under the influence of the autonomic nervous system either by its direct action or as a result of the liberation of hormones, such as

those of the posterior pituitary body or of the adrenals, or by a combination of both nervous and hormonal agencies. We believe that overactivity of this normal mechanism, brought about by various means, may be the origin of numerous pathological renal conditions. We must, however, emphasise that we do not regard a cortical anoxia resulting from excessive diversion of the intrarenal blood flow from the cortex to the medulla as the only cause of the pathological changes found in these various conditions We think it probable that such a cortical anoxia is an important factor at some stage in the development of many pathological renal lesions, but obviously other factors also play a large part in the causation of these lesions We suggest that it is the different natures of these other factors which, together with the cortical anoxia, account for the variations in the distribution and character of the lesions which are found

A stage beyond the inhibition of diuresis by emotion, described above, and almost certainly originating in overactivity of the same centres, is to be found in cases of hysterical anuria (Charcot, 1877). Further, the anurias which occur after various forms of stimuli to the urinary tract, such as the passage of a ureteric stone, the handling of the ureters during operation, or catheterisation, are undoubtedly due to the operation of a reflex mechanism, and it seems more than likely that the effect of this reflex activity is a wellnigh complete diversion of the intrarenal blood flow from the cortex to the medullary pathway

Another type of anuria which may find at least some part of its explanation in the results of our experiments is that which occurs in cases of 'crush syndrome' In animals submitted to a form of trauma designed to simulate the crushing injuries of these human cases, we demonstrated a diminution in calibre of the renal artery (Figures 9 and 10) and a diversion of the intrarenal blood flow from cortex to medulla (Figure 65*a*). We believe that these changes in the renal circulation were due, in a considerable part at least, to neurovascular reflexes initiated in the injured limb, since we were able to produce similar changes by the stimulation of various nerves. But in our experiments the trauma was inflicted on anaesthetised animals, and it seems reasonable to expect that in the human cases of crush syndrome, where the effects of acute emotional strain are added to the effects of any neurovascular reflexes initiated in the injured limb, the action of the nervous system on the circulation of the kidney must be enhanced. In the human cases we cannot exclude the possibility that the effects may have been partly due to liberated hormones acting on the vessels of the kidney But in our experiments we found evidence of a direct nervous control of the renal vessels, for in animals in which the splanchnic nerves had been divided before a tourniquet was applied to the thigh no cortical diversion occurred, on the contrary, the cortical blood flow was increased (see Figure 64). Milles, Muller, and Peterson (1932) found

that in dogs renal denervation was followed by a long persisting dilatation of the cortical blood vessels.

Our experimental findings lend support to the theory that renal anoxia or, as we should term it, *cortical anoxia*, plays an important part in the development of the renal failure in cases of crush syndrome. As we envisage it, the diversion of the blood flow from the cortex is not so complete as to result in a total ischaemia, since we are not aware that any case of complete cortical necrosis has been reported in crush syndrome, although foci of severe cellular degeneration may be seen in this condition. Presumably, a limited circulation continues through the cortex, and this is sufficient for nutritional purposes but not for glomerular filtration. The pallid cortex with its ischaemic glomeruli and the congested medulla, seen in the kidneys of crush syndrome cases at necropsy (Bywaters and Dible, 1942), favour this explanation of the cause of the anuria. In favour also of this suggested explanation is the fact that in patients who recover from this condition the renal function returns to normal. The secretion of urine may be resumed with dramatic suddenness, a phenomenon which could well be explained by the sudden resumption of a full cortical circulation. However, we agree with Eggleton, Richardson, Schild, and Winton (1943) in their conclusion that it is unlikely that any single factor provides the explanation for all the renal changes found in crush syndrome.

Darmady (1947) reports seventeen cases, of which five recovered, of a syndrome of 'traumatic uraemia'. This syndrome is obviously closely related to the crush syndrome, although in these cases the trauma was not, with one exception, a crushing one, but in all cases was due to severe wounds, mainly of the lower extremities, and in many cases major vessels were damaged. All the patients had suffered considerable haemorrhage and many showed a hypotension for considerable periods. Anuria occurred in one case and oliguria in all, as did also a rise in blood urea, and it is of interest that once uraemia was apparent the blood pressure was frequently raised. In the patients who recovered this rise was less marked than in the fatal cases, and it was noted that when the level of the blood urea fell, after about six to eight days, it fell with a dramatic suddenness, suggesting that a crisis had occurred. It would be of interest to know whether at this stage the output of urine increased as dramatically as the level of the blood urea fell. The pathological changes seen in the kidneys of the fatal cases included a yellow, glistening cortex, and histological changes similar to those recorded in cases of crush syndrome. Darmady, Siddons, Corson, Langton, Vitek, Badenoch, and Scott (1944) refer to congestion of the medulla in the cases of traumatic uraemia which they report.

The fact that relatively few patients develop traumatic uraemia, or succumb to a condition resembling this syndrome, may well be due to the rarity with

which all the factors necessary to cause the syndrome are operative at the appropriate times. In addition, it seems probable that the susceptibility of the individual subject to these factors plays an important part in determining whether the syndrome develops or not. Our studies have shown how variable may be the degree of response shown by different animals subjected to the same experimental procedures. We attributed the variations in the results of identical experiments to differences in the susceptibility of the individual animals, but it seems possible that the presence or absence of other factors of which we were unaware may have contributed to the differences in the results obtained.

In cases of crush syndrome, traumatic uraemia, and similar conditions in which cortical anoxia appears to be a feature, the use of the 'artificial kidney' (Kolff, 1946, *a*, *b*) or peritoneal dialysis (*Lancet*, 1947) seem to offer valuable means of tiding the patient over the period during which, as we interpret it, the renal cortex is excluded from the circulation as a result of diversion of the intrarenal blood flow.

Changes in both the function and the morphology of the kidney somewhat similar to those observed in both crush syndrome and traumatic uraemia may be seen in a number of other conditions; for instance, in cases of incompatible blood transfusion (De Navasquez, 1940; Foy, Altmann, Barnes, and Kondi, [illegible], 1943), septic abortion (Bratton, 1941), [illegible] Young, 1942), Weil's disease (Wylie, [illegible] kidney (Peterson and Finland, 1941), blackwater fever (Foy, Altmann, Barnes, and Kondi, 1943; Maegraith, 1944), and cholera (Chatterjee, 1941). Foy, Altmann, Barnes, and Kondi (1943), in a most interesting discussion on the aetiology of the renal failure which occurs in cases of crush injury, incompatible blood transfusion, and blackwater fever, suggest that the renal changes found in all these conditions have a similar basis. They emphasise that dehydration is the most constant feature observed in patients showing these syndromes. They conclude that the anuria associated with these conditions is due not so much to blockage of the tubules, as is suggested by some workers,[1] as to diminution in the blood volume, in the renal circulation, and in glomerular filtration. They believe that variations in renal blood flow are much more important in controlling glomerular filtration than are changes in blood pressure Moreover, they point out that reduction in blood flow will affect the tubules even more than the glomeruli, since the amount of work done and oxygen consumed by the tubular cells is vastly greater than is the work and oxygen consumption of the cells of the glomerular epithelium. Maegraith (1944), in a discussion of blackwater fever anuria, points out the contrast between the relatively

[1] The examination of tubules in continuity, as practised by Oliver (1944-45) would appear to offer a far more satisfactory means of assessing the part played by tubular blockage in causing renal failure than is possible by the ordinary methods of histological examination, upon which most workers have based their views

anaemic cortex and the congested medulla, which is found in fatal cases. Similarly, bloodlessness of the glomeruli and engorgement of the medulla was reported by Turnbull (1929) in a case of fatal blood transfusion reaction. Maegraith and Findlay (1944) suggest that the degenerative changes seen in the cells of the tubules may be due to anoxia resulting from a by-passing of the blood flow through the cortex. Thus, they envisage the possibility of a redistribution of the renal blood flow, but they make no suggestions as to the precise nature of this redistribution. The anuria of cholera was believed, by Cohnheim, as long ago as 1882, to be due to spasm of the renal arteries, and Tomb (1942) suggested that the pathological changes in the kidneys in this disease were due to anoxia, the explanation which he offered for the changes in crush syndrome (Tomb, 1941).

We have ourselves had no opportunity to examine the material from the kidneys of patients who have died from these various conditions, and it is extremely difficult to determine from the reports of some workers whether their findings are compatible with the theory that diversion of the blood from cortex to medulla, such as we have demonstrated in experimental animals, is one of the aetiological factors concerned. For the proving or disproving of our thesis it is essential to know whether the pathological changes seen were in the cortex or in the medulla; it is not sufficient merely to be told, for example, that the change was present in the loop of Henle for, as can be seen in Figure 54, loops of Henle lie both in the cortex and in the medulla, and the location of the pathological lesion, whether in medullary ray or in medulla proper, must be known before one can assess its possible relation to the diversion theory.

The most striking evidence that the diversion of the blood flow from cortex to medulla which we have demonstrated in our experimental animals occurs also in man is provided by the pathological condition of bilateral cortical necrosis of the kidney This condition is comparatively rare and, although a considerable number of careful morphological studies have been made, its aetiology is still uncertain. Duff and More (1941) give a valuable review of the clinical and pathological features of the seventy-one cases which had been reported in the literature up to that date; forty-eight of these cases were associated with pregnancy. In an interesting paper Dunn and Montgomery (1941) report a further fifteen cases, seven of which were associated with pregnancy. They describe in detail the morbid anatomical changes in the kidneys of the eight cases of the series in which the condition, which they term an 'acute necrotising glomerulonephritis', was not associated with pregnancy.

Doniach and Walker (1946) report a case of bilateral cortical necrosis, combined with necrosis of the pituitary body, after concealed accidental haemorrhage. The macroscopic appearance of one of the kidneys from this

case is seen in Figure 73. The cut surface shows that the cortex is pale and necrotic throughout a great part of its width The necrotic zone, which

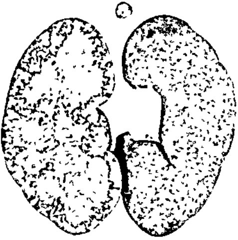

FIG 73 Photograph of right kidney and pituitary body from a human case of bilateral cortical necrosis of the kidney (from Doniach and Walker, 1946) Note that the cut surface (seen on the left) shows a superficial pale zone of necrosis of irregular width, bordered on its deep aspect by a narrow band of hyperaemia The medulla is congested Compare with Figures 67*b* and 70, which show a similar cortical necrosis in rabbits Difference in the age of the infarcts accounts for the difference in the colour of the infarcted zones in the human and rabbit kidneys

includes the columns of Bertini, is edged on its deep aspect by an irregular line of reactive hyperaemia, which appears to encroach nowhere upon the medulla The medulla itself is congested This picture is characteristic of the condition, except that the subcapsular zone of hyperaemia which is in fact present is not well seen. A good coloured illustration of a macroscopic specimen of a kidney from a case of bilateral cortical necrosis in pregnancy may be seen in Scriver and Oertel's (1930) paper, and this shows clearly the hyperaemic subcapsular zone.

The appearances seen in the human kidney illustrated in Figure 73 should be compared with the appearances of kidneys of rabbits in which cortical necrosis was produced by an injection of staphylococcus toxin, illustrated in Figures 67*b* and 70. It will be noticed that in all these cases of cortical necrosis, all that survives is an 'inner kidney' with a thin shell of cortex. The dark colour of the infarcted cortex seen in Figure 67*b* contrasts with the pale colour of the infarcted cortex illustrated in Figure 73 and is due to the fact

that the infarction in the former case was very recent, only thirteen hours having elapsed since the toxin was injected. In the human case (Figure 73), the age of the lesion was thought to be about six days.

When a kidney of a patient with bilateral cortical necrosis is examined microscopically the pale area is seen to be necrotic throughout and to make up the outer half or two-thirds of the cortex. It is bordered on each side by an inflammatory zone. In striking contrast to the pale infarcted zone with its inflammatory borders, the cortex in the underlying juxtamedullary zone is living and relatively normal, as is also the medulla. The small arteries in the necrotic zone show almost invariably either some pathological change in their walls or occlusion of their lumina by some form of thrombus, or both. The thrombi may be composed of fibrin, platelets, or conglutinated red cells (Duff and More, 1941). Proximal (deep) to the necrotic area of the cortex the main arteries are patent. In the juxtamedullary zone of the cortex the glomeruli (including those which we term juxtamedullary glomeruli—see Chapter IV) are described by

mention changes suggestive of

1941). Russell (1929) points

seen in nephritis, that is, focal necrosis of the tuft and adhesions, may be seen in the borders of infarcts. Dunn and Montgomery (1941) attribute the absence of thrombi in the larger intrarenal arteries in cases of cortical necrosis to the fact that a circulation continues through the proximal parts of the interlobular arteries (which they term intralobular arteries). The continuance of the circulation through these vessels is, they think, explained by the easier escape which is afforded to the blood by the deep glomeruli, whose efferent vessels pass by short routes direct to the medulla and not to the cortical rete. They do not enlarge further on this point.

Thus, in bilateral cortical necrosis of the human kidney we have a pathological condition in which the more peripheral parts of the cortex undergo a necrotic sequestration (Scriver and Oertel, 1930), while the deepest zone of the cortex and the whole of the medulla survive (in only five out of the seventy-one cases reviewed by Duff and More, 1941, was the necrosis seen to involve the medulla, and then only slightly and in small focal areas). In this condition, therefore, we have convincing evidence that in the human kidney the medullary pathway carries the intrarenal blood flow when this is prevented from circulating through the cortex, as we have seen it to carry the diverted cortical blood flow in our experimental animals (Figures 18–20, 23, 67, 70, 71). For in these cases of human bilateral cortical necrosis, in striking contrast to the occluded vessels of the outer cortex, with their damaged walls and the necrosis of this zone of the kidney, the vessels forming the medullary pathway are filled with normal red blood cells, and both the walls of these vessels and the other medullary tissues are living and show minimal pathological changes. The

contrast between the necrotic cortex and the living medulla is particularly striking in those cases in which histological as well as clinical evidence shows that the cortical necrosis is of several days' standing, as in the case described by Doniach and Walker (1946) and illustrated in Figure 73.

The results of our experiments probably explain what happens in the initial stages of the vascular disturbances which result in the human condition of bilateral cortical necrosis. For in these experiments we saw that the arteries in the peripheral parts of the cortex were peculiarly reactive, constricting more readily in response to various forms of stimulation than the more proximal parts of the renal arterial tree. In some instances we saw that as a result of such constriction the intrarenal blood flow had no passage open to it through the arteries of approximately the outer two-thirds of the cortical zone but the arteries in the deepest zone of the cortex were relatively unaffected by the constriction In consequence, the blood which was denied access to the cortical pathway was able nevertheless to make an intrarenal circuit through the medullary by-pass (see Figures 21, 67, 71) We suggest that a similar constriction of the arteries in the peripheral parts of the cortex takes place in the early stages of bilateral cortical necrosis in the human subject. In experimental animals susceptible to staphylococcus toxin we have seen a striking blanching of the surface of the kidney occurring shortly after the intravenous injection of the toxin (see Chapter V) We interpreted this blanching as being due to intense constriction of the arteries of the peripheral zone of the cortex. Further, we concluded that this intense constriction was limited to the arteries of the peripheral cortical zone, because blood continued to flow through the renal vein during the period of cortical pallor. Indeed, in some cases, while this pallor persisted, the blood passing through the renal vein became arterial in colour and its flow was clearly seen to be pulsatile. These observations indicated that as a result of constriction of the arteries of the peripheral parts of the cortex, the intrarenal blood flow had been diverted through the channels of the medullary by-pass In view of the fact that an injection of staphylococcus toxin in the rabbit results finally in the development of a bilateral cortical necrosis of the kidney which is fundamentally similar, both macroscopically and microscopically, to the bilateral cortical necrosis of the human kidney, it seems probable that the constriction of the arteries in the peripheral parts of the cortex of which we saw evidence in our experimental animals occurs also at an early stage in the development of the human condition This suggestion appears to be at variance with the views of Oertel (Scriver and Oertel, 1930), De Navasquez (1938), and Dunn and Montgomery (1941) who, because of the dilatation of the interlobular arteries and the congestion of the glomerular tufts in the necrotic zone seen histologically, do not consider that vascular spasm plays a part in the produc-

tion of the condition. We suggest, however, that this dilatation is due to a vasoparalysis which follows an initial vasospasm of extreme intensity.

Very few cases of bilateral cortical necrosis of the kidney with recovery have been reported in the literature. This is probably due to a hesitation on the part of clinicians to make a definite diagnosis of this condition on clinical grounds alone and without the confirmation provided by histological evidence. Undoubtedly such cases are seen more frequently than the number reported in the literature suggests. However, a few cases in pregnant women have been described in which the history, clinical signs, and course of the disease during the first week are so similar to those of cases ending fatally, and in which the condition has been confirmed at necropsy, that there seems every reason to accept them as genuine, but less severe, cases of cortical necrosis. O'Sullivan and Spitzer (1946) found only nine cases of recovery in the literature, and described two further cases which recovered after splanchnic block.

It seems probable that in these patients who recover from cortical necrosis of the kidney we have examples of a redistribution of the intrarenal blood flow, with a diversion from cortex to medulla, similar to that which is seen to have occurred in the kidneys of patients who have died from this condition. In the patients who recover, however, we suggest that the constriction of the peripheral segments of the renal arterial tree is less intense than in the cases which prove fatal and that consequently, despite a considerable diversion, the cortical blood flow and head of pressure are sufficient to maintain vitality but are inadequate for glomerular filtration. Presumably, the onset of diuresis, marking the first stage in the recovery of the patient, follows a relaxation of the constriction of the cortical vessels, which is not succeeded by the vasoparalysis of the more severe cases.

Penner and Bernheim (1940), during an investigation into the mechanisms of shock, found that they could produce renal lesions in dogs by the intraperitoneal injection of epinephrine (adrenaline). These lesions resembled the lesions of bilateral cortical necrosis seen in man. They concluded that vasospasm, especially of the afferent arterioles of the glomeruli, was the cause of the lesions, and as a result of a study of two human cases they concluded that the vasospasm of profound shock could be sufficiently prolonged and intense to cause necrotic lesions. Black-Schaffer, Hiebert, and Kerby (1947) have shown that bilateral cortical necrosis can be produced in rabbits by injections of washed living meningococci, and attribute its development to a generalised Shwartzman reaction. They think it possible that the Shwartzman substance acts on the interlobular arteries causing severe vasoconstriction. Rohrer (1932) records the production of cortical necrosis of the kidney in pigs as a result of the administration of large doses of the virus of hog cholera, but he considers the necrosis to be due to changes in the arterial walls rather than to vasoconstriction.

We have referred to the production of cortical necrosis in animals of different species, reported by other workers, because it seems to us that the living medulla, which is seen in this condition in the kidneys of various mammals, is a suggestive indication that the use of the medullary pathway as a by-pass for blood diverted from the cortex is a feature characteristic of the circulation of the mammalian kidney.

In connection with any discussion of bilateral cortical necrosis it is interesting to consider the results which Byrom (1937) obtained in rats as a result of injections of pitressin It will be remembered that the antidiuretic principle of the posterior pituitary cannot as yet be separated from the pressor principle (Goodman and Gillman, 1941), and that pitressin is a commercial posterior pituitary preparation not assayed for (though possessing) antidiuretic activity, but assayed for pressor and oxytocic activity

Byrom found that large doses of pitressin, injected subcutaneously, caused ischaemic arterial infarcts in the cortex After very large doses in small animals, adjacent areas of necrosis were sometimes fused and the appearance closely resembled that seen in massive cortical necrosis (bilateral cortical necrosis). Byrom attributed the cortical necrosis to arterial spasm, since the vessels of the infarcted area were free from thrombus Moreover, on opening the abdomen shortly after he had injected a large dose of pitressin, he had found that the surface of the kidneys showed conspicuous areas of pallor (an observation which we have ourselves confirmed) and, using a hand lens, he had seen that the glomeruli in these areas were blanched As a result of injections of smaller doses repeated for several days, he noted that the kidneys might be either uniformly pale, or else mottled and showing poorly defined areas of pallor. Histologically, necrosis was either absent or limited to isolated cells or groups of cells, its place being taken by more or less severe degenerative changes of the convoluted tubules, particularly of the first convoluted tubules The glomeruli nearly always appeared normal It is of interest that the changes seen by Byrom in the renal cortex of the rats of this latter group were remarkably similar to the changes which Scarff and Keele (1943) observed in the kidneys of rabbits after temporary complete occlusion of the renal artery Byrom (1937) considered that the less severe degeneration which occurred after injections of the smaller doses of pitressin was the result of a milder degree of the arterial spasm which, after large doses, had been sufficiently intense and prolonged to cause actual infarction

Byrom's interpretation of the results of his experiments closely resembles the interpretation which we gave to our own findings in experiments of a somewhat similar character (see Chapter III) For we concluded that the immediate effect of posteri
to constrict the arteries in
blood to be diverted fro

by-pass. Our observations were confined to acute experiments and we made no histological studies in this particular series, but Byrom pointed out the similarity of the lesions produced in his rats by injections of vasopressin with those seen in cases of bilateral cortical necrosis of the kidney, eclampsia, and malignant hypertension. He did not, however, seem to feel that there was sufficient evidence to prove that vascular spasm and/or oversecretion of the pressor substance of the posterior pituitary hormone were necessarily the cause of the lesions seen in this group of pathological conditions. Wakim, Herrick, Baldes, and Mann (1942) found that pitressin, injected intravenously into frogs, caused a blanching of the glomeruli and a complete cessation of the glomerular blood flow. They also injected pitressin into dogs by various routes, in a dosage infinitely lower than that used by Byrom in rats or by ourselves in rabbits and rats. They found that intravenous injections resulted in anuria and in a reduction in renal blood flow, as measured by a thermostromuhr. The observations of these workers appear to support our view that the immediate effect of pitressin is a vasoconstriction in the peripheral cortex, resulting (in the dog) in diversion of the intrarenal blood flow from the cortex through the medullary by-pass, with a consequent reduction in glomerular filtration.

Griffith, Corbit, Rutherford, and Lindauer (1941) found that pitressin injected intraperitoneally into rats caused hypertension. In view of the cortical pallor which both Byrom (1937) and we ourselves observed after the administration of pitressin, it seems probable that the pitressin hypertension reported by Griffith and his colleagues was due to a peripheral vasoconstriction in which the arterial vessels of the peripheral parts of the renal cortex were among the more important of those involved.

Lastly, we come to a consideration of hypertension, a condition which constitutes one of the most serious problems facing civilised man at the present time. Goldring and Chasis (1944) have estimated that in the United States this condition accounts annually for more than one-third of the total number of deaths.

Richard Bright (1827) in his 'Reports of Medical Cases' pointed out that an enlarged state of the heart might be accompanied by a highly diseased condition of the kidneys and an albuminous urine. Ever since Bright's day the part played by the kidney has come to be recognised more and more as an important factor in the aetiology of hypertension. It is now clear that organic renal disease precedes the onset of hypertension in a considerable number of cases, but there is a large group of cases in which organic renal disease is not an obvious precursor of the hypertension. This group comprises the cases of so-called 'essential' hypertension.

We shall make no attempt to survey the vast literature of nephritis and

hypertension, for the whole field is covered in recent monographs and lectures (see Russell, 1929; Berglund and others, 1935; Goldblatt, 1937–38; Fishberg, 1939; White and Smithwick, 1941; Ellis, 1942; Goldring and Chasis, 1944; Bell, 1946; Braun-Menéndez and others, 1946; Goldring and others, 1946, Goldblatt, 1947) The work of Goldblatt, Lynch, Hanzal, and Summerville (1934) marks an epoch in the experimental investigation of essential hypertension They showed that transient hypertension could be produced in dogs by the constriction of the main renal artery of one kidney with an adjustable silver clamp By moderately constricting both renal arteries, or alternatively by constricting one renal artery and removing the opposite kidney, they were able to produce permanent hypertension, unaccompanied by disturbance of renal excretory function. Later, Goldblatt (1938) reported the production in dogs of a malignant phase of this type of experimental hypertension by excessive constriction of the main renal arteries. These animals died of ren high degree of hypertension Goldblatt nal ischaemia resulting from the constrictic and Pickering (1938) produced hypertension in rabbits by constricting one renal artery and removing the other kidney, or alternatively by constricting both renal arteries. Wilson and Byrom (1941) produced long-sustained hypertension in rats by the partial constriction of one renal artery, the other kidney being left intact. Verney and Vogt (1938), as a result of experiments on dogs in which they obstructed the blood supply to one or both kidneys by a modification of Goldblatt's clamps, concluded that the presence of ischaemic renal tissue was an indispensable condition for the development of renal hypertension. These workers found that hypertension developed even when the ischaemic kidney was completely denervated, thus showing that the hypertension was not due to afferent impulses carried from the kidney either to the vasomotor centre, or to other centres in functional connection with organs capable of influencing arterial pressure They concluded sion was caused by the formation tensive substance which escaped in that sympathectomised dogs developed hypertension after obstruction of their renal arteries, an observation which suggested that the hypertensive substance liberated by the ischaemic kidney had a direct action on the muscle of the walls of the peripheral vessels. It is of interest that in these sympathectomised animals the blood pressure, whilst remaining markedly raised, showed fluctuations from day to day, and that exercise was, at least in one case, always followed by a large fall in blood pressure.

From the results of these and of many other investigators (see Goldblatt, 1947), there is ample evidence that the ischaemic kidney produces and liberates into the blood stream a pressor substance which acts directly on the

smooth muscle of vessels, causing a constriction of the peripheral vascular bed and a consequent rise of blood pressure

The production of a pressor substance by the ischaemic kidney as a result of clamping the renal arteries of experimental animals explains those cases of human hypertension in which the renal arteries are obstructed by atheromatous plaques, by external pressure, or by similar mechanical means. A remarkable case is reported by Cook and Pearson (1946) of a young man whose renal arteries had been completely occluded by atheroma and thrombosis, the renal blood supply apparently being maintained by capsular vessels. The renal function was comparatively good, and at necropsy the kidneys were found to be remarkably free from pathological change, both on macroscopic and microscopic examination. Here, clearly, was a natural bilateral application of Goldblatt clamps. However, the number of cases of hypertension in man in which the condition can be attributed to a permanent reduction in calibre of main renal arteries by mechanical obstruction is small, and such an aetiological factor can be discounted as a cause for the majority of cases of essential hypertension.

What, then, in these latter cases constitutes the Goldblatt clamp, and where is it situated? In other words, what is the mechanism which causes the ischaemia of the kidney and the consequent formation and liberation of the pressor substance responsible for the hypertension? The results of our experiments suggest a mechanism which may constitute a functional 'clamp'. Is it possible that diversion of the intrarenal blood flow from the cortical pathway through the medullary by-pass causes a cortical ischaemia of sufficient degree to result in the formation and liberation of the pressor substance?

Goldring and Chasis (1944) consider that renal arteriolosclerosis does not precede the development of essential hypertension, although it is a concomitant or consequence of hypertension Castleman and Smithwick (1943) examined renal biopsy specimens from one hundred hypertensive patients, and concluded that the evidence of renal vascular disease in more than half of the cases was inadequate to prove this to be the sole factor in producing the hypertension; they thought that in many of these cases hypertension preceded the renal vascular lesion. Castleman and Smithwick's work is open to criticism, in that the condition observed in the small biopsy specimen did not necessarily represent the condition of the kidney as a whole, but it seems that their conclusions were correct.

Much work has been done on the chemical and other aspects of the pressor substance elaborated by the kidney and the subject is discussed in full by Braun-Menéndez, Fasciolo, Leloir, Muñoz, and Taquini (1946). Cruz-Coke (1946) has shown that lack of oxygen is of vital importance at certain stages in the formation of the pressor substance, but has looked in vain for the

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But, whilst all investigators seem to be agreed that hypertension of renal origin is due to some humoral pressor substance formed in the kidney, it has not yet been definitely established where in the kidney this substance is produced. On the whole, opinion seems to favour the renal cortex as the source of the pressor substance Goormaghtigh (1944, 1945, *b*) has described granular, afibrillar cells in the walls of the arterioles of the renal cortex and in the juxtaglomerular apparatus, and as he found that these cells were larger and more numerous in experimental animals with renal ischaemia (Goormaghtigh, 1940) he suggested that they secreted and liberated a pressor substance. Goormaghtigh (1945, *a*) also observed enlargement of these cells in the kidneys of fatal cases of crush syndrome Kaufmann (1942) found hypertrophy of the same cells in the kidneys of patients with hypertension. Friedman and Kaplan (1943) believe, on the other hand, that the pressor substance is formed in the cells of the proximal convoluted tubules.

If, then, the pressor substance is formed in cells situated in the renal cortex, and if anoxia is an essential condition for its production, it follows that the pressor substance will be formed when the cortex becomes ischaemic. It seems possible, therefore, that excessive diversion of the intrarenal blood flow from the cortex through the medullary by-pass may be an initiating factor in the production of the pressor substance and thus in the development of human essential hypertension Our experimental work has shown that such a diversion of the blood flow can be produced by a constriction of the peripheral arteries of the cortex and that this constriction can be caused by a nervous or hormonal agency Our studies have indicated the peculiar sensitivity to stimuli of the peripheral arterial vessels of the cortex in the experimental animal, and it seems probable that in man also nervous or hormonal stimuli may, in appropriate circumstances, effect a similar response from these vessels, and thus cause diversion of some of the cortical blood flow. It is significant that the ischaemic atrophy characteristic of the kidney in the late stages of essential hypertension predominates in the outer third of the cortex (Russell, 1947) Smith (1939–40) was convinced that renal vasoconstriction of psychogenic nature was responsible for the disturbances recorded in his tests of renal function on frightened men, which have been referred to earlier in this chapter We should like to suggest that the vasoconstriction in these cases affected mainly the vessels in the peripheral parts of the cortex and that, as a result of this vasoconstriction, a considerable proportion of the intrarenal blood flow was diverted from the cortex through the medullary by-pass. The possibility that psychogenic renal vasoconstriction may be a factor in the aetiology of human essential hypertension has been recognised by various workers, and a consideration of the psychological factors in essential hyper-

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tension is given by Weiss (1942). Nevertheless, there is considerable difference of opinion as to whether the nervous system is of aetiological importance in this condition.

Garai (1945) found that shipwrecked mariners who had suffered prolonged immersion tended to have a raised blood pressure and that they showed increased vasomotor reactions (as gauged by the cold pressor test). He suggested that the reflex constriction of the vessels of the kidney, known to be caused by exposure to cold, had played a part in producing the hypertension. Medoff and Bongiovanni (1945) and Farris, Yeakel, and Medoff (1945) found that they were able to produce a persistent hypertension in rats by stimulating them repeatedly with intense noise. Heymans (1939) and Grimson, Bouckaert, and Heymans (1939) record the production of a sustained hypertension in dogs, from which they had removed the moderator nerves and the entire sympathetic nervous system, with the exception of the innervation of the kidneys and adrenals. Subsequent denervation of the kidneys resulted in a restoration of normal blood pressure. They concluded that the hypertension in these dogs was due to overactivity of the sympathetic nerves of the kidneys. Since sympathetic denervation had been complete elsewhere, it appears that the hypertension must have been caused by the release of some pressor substance from the stimulated kidney, which raised the blood pressure by a direct constrictor effect on the peripheral vessels.

Our own investigations have not as yet included any studies of hypertension produced in the experimental animal. We are not in a position, therefore, to contribute to the problem of essential hypertension on the basis of experiments designed to determine the aetiological factor. However, in our studies of human kidneys by injection methods we observed that in the kidneys of elderly persons and of those suffering from Bright's disease (Ellis, 1942) many of the juxtamedullary glomeruli showed unusual features, which we interpreted as being due to some form of degenerative process (see Figure 74, and also Figures 58 to 61). In Chapter IV we described these abnormal glomeruli in some detail, and we also offered a suggestion as to their possible evolution. At this point we must refer again to these degenerate juxtamedullary glomeruli because, in view of the influence which they must have upon the intrarenal haemodynamics, they may be an important factor in the development of a permanent hypertension.

In studying the vasculature of human kidneys by injection methods, it was noteworthy that in some kidneys we obtained a much better filling of the medullary vessels than in others. As we mentioned in Chapter IV, in normal kidneys an injection introduced from the arterial side resulted in a good filling of the vessels of the cortex and a relatively poor filling of the vessels of the medulla. In contrast to this finding, similar injections introduced into many pathological kidneys and into kidneys from patients of an advanced age

resulted in a less complete filling of the cortical vessels and an unusually good filling of the vessels of the medulla. The easier filling of the medullary vessels in pathological kidneys, an observation that was also made by Gross (1917, 1918) in contracted kidneys, suggests that in certain pathological conditions the vascular channels of the medulla take a greater proportion of the intrarenal blood flow than is normally the case. This suggestion is confirmed by the hyperaemic appearance of the medulla which is seen when a contracted kidney is sectioned at necropsy, an appearance which is well illustrated in some of Bright's (1827) beautiful colour plates The relatively prominent medulla of the contracted kidney, contrasting with its shrunken cortex, is a further indication that the blood supply of the medulla has remained ample whereas that of the cortex has suffered great reduction.

We have shown that the vasa recta, the predominant vessels of the medulla, constitute the greater part of a medullary by-pass and that they derive their blood supply from the juxtamedullary glomeruli. We have confirmed the views of Bowman (1842) and of many subsequent workers that in the normal kidney all the blood which circulates through the organ passes through g[illegible] than that which e[illegible] ncrease in blood f[illegible] ised blood flow through the juxtamedullary glomeruli

When we examined neoprene casts of the vascular tree of human kidneys in which the vessels of the medulla were unusually well filled we found that many of the juxtamedullary glomeruli were of degenerate type. The exceptionally good filling of the medulla was clearly associated with the presence of these abnormal glomeruli

On close scrutiny of the casts of the degenerate juxtamedullary glomeruli, the explanation of the good medullary filling became apparent For we saw that in each case the aff[illegible] continuous trunk, being [illegible] ing capillary loops of the [illegible] from one side of this trunk (Figure 74) Thus, in these cases there was easy access to the vasa recta through vessels of large calibre, and the injection mass was therefore able to pass directly from the basal parts of interlobular arteries through the medullary by-pass without passing through the retia mirabilia of glomerular tufts. MacCallum (1939) has described similar degenerative glomeruli and has given some account of the cellular changes around the glomerular tufts.

We have suggested in Chapter IV that these degenerative changes in the juxtamedullary glomeruli are due, in the first instance, to excessive diversion of the intrarenal blood flow from the cortex through the medullary by-pass. The juxtamedullary glomeruli, as we have shown, form the entrance into

the medullary by-pass and, as we envisage it, the increased use of this by-pass causes a dilatation of one of the capillary loops of these glomeruli, such as that seen in Figure 58*b* and Figure 61. We have no knowledge as to whether the diversion which causes the dilatation is unusually prolonged in duration, or whether the volume of the blood diverted is unusually great, or even whether both of these factors are needed to cause the initial capillary dilatation. However, once one capillary loop of the glomerulus has become larger in calibre than the remaining loops, it will tend to carry more blood than the others and it will also tend to dilate further, because the increased circumference of its wall will render it less able to withstand pressure. Consequently, when next blood is diverted from the cortex through the medullary by-pass and the pressure in these channels is raised, a further dilatation will occur and the dilated loop will carry an even greater proportion of the blood flow than previously. As the progressively dilating capillary carries more and more blood, the other capillaries of the tuft carry less and less, and in consequence gradually atrophy until only the dilated 'capillary' is left, and the proximal part of the 'arteria recta vera' of the earlier writers is formed. Casts of fully-developed 'arteriae rectae verae' show that these trunks are often of remarkably large calibre. In Figure 58 we show a series of neoprene casts of degenerate juxtamedullary glomeruli which illustrate the progress of degeneration. Further examples may be seen in Figures 59 to 62.

We have suggested above the possibility that diversion of the intrarenal blood flow from the cortex through the medullary by-pass may be an initiating factor in the production of hypertension. It seems also possible that the changes which we have just described in the channels which form the first

FIG 74 Stereoscopic photomicrographs of neoprene cast of degenerate juxtamedullary glomerulus from kidney of man aged 73 Note the continuous trunk of large calibre formed by the afferent and efferent vessels, showing the characteristic sharp bend at the site of the glomerulus. The few glomerular capillaries which remain are attached to the convex side of this bend

stage of this by-pass may provide an explanation for those cases in which hypertension becomes an established condition. For, as a result of these changes, the blood can now make an intrarenal circuit through a medullary pathway which is of large calibre from beginning to end. The resistance normally encountered in this pathway has been removed by the replacement of the glomerular capillary tuft by a single vessel of large calibre, whereas the resistance encountered in the cortical pathway remains unchanged or is even increased. As more and more juxtamedullary glomeruli undergo these changes, and as the changes become more pronounced, the medullary pathway inevitably takes an increasing proportion of the blood reaching the kidney, and the cortex is correspondingly deprived of its blood supply. Thus, whereas normally the medullary pathway appears in most instances to serve passively as a by-pass for the diverted cortical blood flow, now, as a result of its changed morphology, this pathway itself diverts the cortical blood flow and, moreover, it causes a *permanent* diversion. No procedure can at this stage increase the blood supply to the ischaemic cortex save an increase in blood pressure, and even with a raised blood pressure much of the increased circulation will be drained away through the medullary pathway before it reaches the cortex.

We have been impressed by the frequency with which juxtamedullary glomeruli of degenerate type are seen in the kidneys of patients with a raised blood pressure. The illustrations of dissected kidneys given by Oliver (1939) and Loomis (1936) show how commonly these workers found 'arteriae rectae verae' in their cases of chronic Bright's disease. But the full significance of these vessels only becomes apparent when one appreciates the fact that they provide easy access to the medullary by-pass, thus opening a permanent shunt and drawing off much blood which would otherwise traverse the cortex.

The dispute as to the existence of 'arteriae rectae verae' as a normal feature of the vasculature of the kidney dates back to the time of Virchow (1857). As the result of his studies of injected human kidneys, he was convinced that there were vessels passing into the medulla which were not related to glomeruli, namely, 'arteriae rectae verae', and he illustrated them clearly. He pointed out that the best example proving his view was provided by the kidneys from a case of amyloid disease, in which he found great numbers of these vessels. This finding probably explains the controversy which has raged as to whether these vessels do or do not exist. For one school of thought has based its views on observations made on pathological kidneys and has regarded the findings as applying equally to the normal kidney, as did Virchow, whereas another school has based its views on observations made on normal kidneys. We have ourselves had the opportunity of injecting and examining the kidney from a case of amyloid disease and, like Virchow, we were impressed by the unusual

profusion of 'arteriae rectae verae'. It was of special interest to us to note in this kidney the great reduction in the number and size of the capillary loops of the cortical glomeruli. Moreover, the amyloid deposits in the cortical glomeruli which had caused this reduction had withstood the action of the acid used for macerating the specimen and were clearly seen. We concluded that the mechanical obstruction of the cortical glomerular capillaries caused by these deposits had been the primary factor responsible for a continuous and increasing diversion of the intrarenal blood flow through the medullary bypass, a conclusion which was supported, in our view, by the presence of innumerable 'arteriae rectae verae'. Goldblatt (1946) and Bell (1946) point out that amyloidosis is often accompanied by hypertension, and that in cases in which the blood pressure is not raised the absence of hypertension is probably due to the cachexia associated with the condition.

In view of the changes in the vascular architecture of the kidney caused by disease or even by old age, and of the consequent changes in intrarenal haemodynamics, we feel that extreme caution is needed in the interpretation of clearance tests when these are applied to patients whose kidneys may be affected by these changes. This view gains support from the observations of Oliver, Bloom, and MacDowell (1941) which, although of a different nature, were probably related to these vascular changes. They found that the nephritic kidney handles trypan blue by mechanisms different from those of the normal kidney and pointed out that the nephritic kidney may also handle substances used in clearance tests by mechanisms which differ from the normal.

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At the present time hypertensive patients are classified into two main groups, namely, those in whom organic renal disease is recognised by all to be the cause of the hypertension (secondary hypertension), and those in whom no organic renal disease is apparent, and the cause of whose hypertension is obscure (essential or primary hypertension). The fact that such terms as primary, essential, benign, or idiopathic are used in referring to the hypertension of this latter group indicates the prevailing ignorance as to the aetiology of the condition. Many consider that this type of hypertension is not of renal origin, since they do not find in these cases renal lesions adequate to account for the increase in blood pressure.

We believe that the kidney plays a part in the causation of essential or primary hypertension similar to that which it plays in the causation of secondary hypertension and that both types of hypertension have a fundamental factor in common, namely, cortical anoxia. We have seen that ischaemia of the renal cortex can be produced by a means other than sclerosis of the renal vessels. By the use of many experimental procedures, ranging from the application of nervous stimuli to the administration of hormones and toxins,

we have been able to demonstrate in animals a cortical ischaemia of a functional character. Diversion of a variable proportion of the intrarenal blood flow from the cortex to the medulla, effected by constriction of the cortical vessels and/or the opening of the medullary channels, is, we believe, a normal mechanism which, by regulating the secretion of urine, plays a vital part in maintaining under all conditions the constancy of the 'milieu intérieur'. We suggest that excessive operation of this normal mechanism may cause an anoxia of the renal cortex similar to that which results from sclerosis of the vessels.

The sensitivity to a stimulus varies greatly from individual to individual no less in the human subject than in the experimental animal. One can, therefore, envisage the possibility that excessive stimulation of one type or another, applied to persons unduly sensitive to that particular type of stimulus, might result in excessive operation of the normal mechanism by which the blood flow is diverted from the cortex

It seems to us that the development of hypertension of essential type finds a possible explanation in the overactivity of this normal mechanism frequently repeated over a period of many years An aetiology of such a functional nature would account for the absence of any indications of renal disorder until a late stage in the condition The delicate compensatory readjustments of the pressure and flow of the intrarenal circulation would explain the prolonged immunity of the kidney from the effects of the rising blood pressure which may be seen in other organs not endowed with a similar mechanism for circulatory readjustment But, whereas cortical anoxia would appear to be an aetiological factor common to both types of hypertension, there is a fundamental difference in the cause of the anoxia, and this difference is of profound significance In the one type, the anoxia is caused from the outset by organic change, and the condition is therefore, unfortunately, largely irreversible. In the other type, the anoxia is due originally and for a prolonged period to a purely functional disturbance, and in these cases the condition, at least in the earlier stages, should be reversible. This difference in the primary aetiology of the two types of hypertension may be one explanation of the variable results which are obtained from treatment of the disease by various methods, including sympathectomy and irradiation of the pituitary body

If a functional disturbance such as we have suggested can be demonstrated in the earlier stages of human hypertension and can be shown to bear a causal relationship to the rising blood pressure, we shall have a new line of attack on the problem of the prevention of hypertension Goldring and Chasis (1944) write 'Recognition of a preclinical phase of hypertensive disease must await discovery of the primary etiological factors and technics for their demonstration' We are well aware that the primary aetiological factors of hypertensive disease have still to be discovered, but we hope that our studies

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In view of the changes in the vascular architecture of the kidney caused by disease or even by old age, and of the consequent changes in intrarenal haemodynamics, we feel that extreme caution is needed in the interpretation of clearance tests when these are applied to patients whose kidneys may be affected by these changes. This view gains support from the observations of Oliver, Bloom, and MacDowell (1941) which, although of a different nature, were probably related to these vascular changes. They found that the nephritic kidney handles trypan blue by mechanisms different from those of the normal kidney and pointed out that the nephritic kidney may also handle substances used in clearance tests by mechanisms which differ from the normal.

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At the present time hypertensive patients are classified into two main groups, namely, those in whom organic renal disease is recognised by all to be the cause of the hypertension (secondary hypertension), and those in whom no organic renal disease is apparent, and the cause of whose hypertension is obscure (essential or primary hypertension). The fact that such terms as primary, essential, benign, or idiopathic are used in referring to the hypertension of this latter group indicates the prevailing ignorance as to the aetiology of the condition. Many consider that this type of hypertension is not of renal origin, since they do not find in these cases renal lesions adequate to account for the increase in blood pressure.

We believe that the kidney plays a part in the causation of essential or primary hypertension similar to that which it plays in the causation of secondary hypertension and that both types of hypertension have a fundamental factor in common, namely, cortical anoxia. We have seen that ischaemia of the renal cortex can be produced by a means other than sclerosis of the renal vessels. By the use of many experimental procedures, ranging from the application of nervous stimuli to the administration of hormones and toxins,

we have been able to demonstrate in animals a cortical ischaemia of a functional character. Diversion of a variable proportion of the intrarenal blood flow from the cortex to the medulla, effected by constriction of the cortical vessels and/or the opening of the medullary channels, is, we believe, a normal mechanism which, by regulating the secretion of urine, plays a vital part in maintaining under all conditions the constancy of the '*milieu intérieur*'. *We suggest that* excessive operation of this normal mechanism may cause an anoxia of the renal cortex similar to that which results from sclerosis of the vessels.

The sensitivity to a stimulus varies greatly from individual to individual no less in the human subject than in the experimental animal One can, therefore, envisage the possibility that excessive stimulation of one type or another, applied to persons unduly sensitive to that particular type of stimulus, might result in excessive operation of the normal mechanism by which the blood flow is diverted from the cortex.

It seems to us that the development of hypertension of essential type finds a possible explanation in the overactivity of this normal mechanism frequently repeated over a period of many years. An aetiology of such a functional nature would account for the absence of any indications of renal disorder until a late stage in the condition The delicate compensatory readjustments of the pressure and flow of the intrarenal circulation would explain the prolonged immunity of the kidney from the effects of the rising blood pressure which may be seen in other organs not endowed with a similar mechanism for circulatory readjustment. But, whereas cortical anoxia would appear to be an aetiological factor common to both types of hypertension, there is a fundamental difference in the cause of the anoxia, and this difference is of profound significance In the one type, the anoxia is caused from the outset by organic change, and the condition is therefore, unfortunately, largely irreversible In the other type, the anoxia is due originally and for a prolonged period to a purely functional disturbance, and in these cases the condition, at least in the earlier stages, should be reversible. This difference in the primary aetiology of the two types of hypertension may be one explanation of the variable results which are obtained from treatment of the disease by various methods, including sympathectomy and irradiation of the pituitary body

If a functional disturbance such as we have suggested can be demonstrated in the earlier stages of human hypertension and can be shown to bear a causal relationship to the rising blood pressure, we shall have a new line of attack on the problem of the prevention of hypertension. Goldring and Chasis (1944) write: 'Recognition of a preclinical phase of hypertensive disease must await discovery of the primary etiological factors and technics for their demonstration ' We are well aware that the primary aetiological factors of hypertensive disease have still to be discovered, but we ho that our studies

have perhaps provided a clue which may lead to the recognition of the pre-clinical phase of the condition. We believe that these primary aetiological factors will eventually be found in the central nervous system, even in the human mind itself, and that with their discovery will come a complete understanding of the condition known as 'essential hypertension', affording a new hope for the victims of this disease of civilised man.

APPENDIX

Further Observations on the Renal Vascular System

In the course of the morphological studies described in Chapter IV, we observed certain other striking features of the renal vascular pattern. These observations were incidental to the main theme of our studies, and were therefore not included in our account of the morphology of the vessels of the cortical and medullary circulations. However, in view of the implications of some of these findings a brief description and a few illustrations may be of value.

The coiled arterial vessels of the renal sinus

In the kidneys of the various mammalian species that we have examined we have found vessels of a remarkable character in the renal sinus which, in view of their appearance and connections, we call coiled arterial vessels. They are seen adjacent to the external surfaces of the walls of the calyces. They arise from interlobar arteries, and are vessels of relatively large calibre; their destination is always an interlobar artery, either that of their origin or an adjacent one, which they join at some point peripheral to their origin. The most striking feature about them is their amazing tortuosity (Figures 75, 76). These coiled vessels of the renal sinus, running their course in the same plane as the interlobar arteries and veins, give off branches exactly similar to the parent coiled vessels, though sometimes of smaller size. Some of these branch vessels end in interlobar arteries, some form junctional vessels between adjacent coiled vessels (Figures 75*b*, *d*, 76), while others again end in the capillary network of the pelvic mucosa. We have seen these spiral arterial vessels in many normal kidneys, both human and animal, and we have been particularly impressed by their greater tortuosity and complexity in the kidneys of human subjects suffering from pathological renal conditions, especially hypertension.

These vessels are so striking in their appearance that we have been surprised to find no account of them in the literature apart from the description by Spanner (1937), so frequently referred to by subsequent authors. The failure to observe these vessels is probably due to the fact that their characteristic coiled arrangement is only apparent in very thick sections of injected kidneys or in casts made by injections of neoprene or a similar type of mass.

Spanner (1937) gives a drawing of one of these vessels, which he describes as being a part of an arteriovenous anastomotic system. In his drawing he shows short branches passing from the coiled arterial vessel directly into a

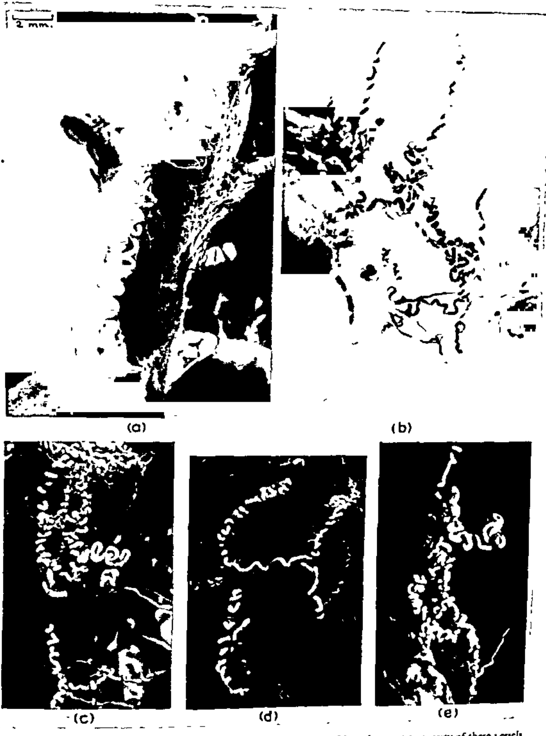

FIG 75 Neoprene casts of coiled arterial vessels of the renal sinus. Note the great tortuosity of these vessels (for description see text) (a) from dog's kidney (b) to (e) from human kidneys (b), (c), and (e) from kidneys of ... at same magnification throughout.)

venous network surrounding the coils. He claims to have found large numbers of these direct arteriovenous communications (360 per square cm.). If such arteriovenous anastomoses were present in the number and situation described by Spanner they would, when open, inevitably deprive the whole kidney of a great part, if not all, of its blood supply, and their functional importance, therefore, could hardly be overrated. But in the large series of kidneys, both animal and human, which we have examined, in spite of the fact that our arterial injections were made at pressures up to 600 mm. Hg, we have been unable to find any evidence that the coiled arterial vessels of the renal sinus give off anastomotic branches which open directly into veins. On the contrary, one of the characteristics of these vessels is the direct communication which they provide between artery and artery.

FIG 76 Thick section of normal human kidney, injected with Indian ink via the renal artery To show coiled arterial vessels of the renal sinus On the right of the field, part of an interlobar artery, in the centre, part of the renal sinus containing coiled arterial vessels, on the left, part of the renal pyramid (Photomicrograph taken with direct lighting)

It appears from Spanner's (1937) paper that his observations were based on the examination of one injected kidney (human), and we suggest that he was misled into describing as anastomotic channels vessels which gave the appearance of uniting artery and vein but which in fact lay in a different plane. Our own studies have made us appreciate the extreme difficulty of determining beyond dispute the presence of an arteriovenous anastomosis in thick mounted sections

Spanner (1937) also described arteriovenous anastomoses both in the cortex and in the capsule of the kidney. We have seen no evidence of the presence in normal kidneys of direct communications between interlobular arteries and veins, as described by Spanner. In the capsule, venous vessels anastomose freely with each other (and also with veins of the perinephric tissues), but we do not believe that arteriovenous anastomoses, even if they exist, are more than an occasional feature. We certainly cannot accept Spanner's count of two hundred and sixty-four arteriovenous anastomoses per square centimetre

The curious finding that the coiled vessels of the renal sinus unite arteries to arteries provokes speculation as to the function of these vessels. We are unfamiliar with interarterial vessels of such large calibre and such unusual form elsewhere in the body, but vessels of large calibre, forming a complex rete, are found joining the internal and external carotid arterial systems of the cat. This rete, which has been described by Davis and Story (1943), is

illustrated in Figure 77, a photograph of one of our preparations of this strange and complex structure. The pattern of this rete and its situation between arteries supplying two different territories suggest that this structure may be concerned in the regulation either of blood pressure or of blood flow between the two territories. It may well be that the coiled vessels of the renal sinus, which also connect artery to artery, have some regulatory function such as that which we have just suggested for the intercarotid arterial rete of the cat. For example, they may be concerned with the regulation of the pressure or flow of the blood supplied to the delicate capillary network of the pelvic mucosa.

Fig 77 Neoprene cast of rete externum of cat Note the complex arrangement of this group of vessels which connects the external and internal carotid arterial systems

The venous junctional vessels of the renal sinus

In the renal sinus there are many vessels of large calibre which unite interlobar veins (Figure 78). The complexity of these venous junctional vessels is most impressive, though their pattern is entirely different from that of the arterial junctional vessels (the coiled vessels of the renal sinus, described above). These venous vessels lie closely adjacent to the outer surfaces of the walls of the calyces of the renal pelvis, and the capillaries of the pelvic mucosa drain into stout tributaries of this complex system. It seems possible that these vessels may provide a clue to the phenomenon of pyelovenous back flow which is sometimes seen after retrograde pyelography (Hinman and Lee Brown, 1924). For, since short stout tributaries of these relatively immobile junctional vessels are connected with the pelvic mucosa, excessive distension of the renal pelvis may well result in rupture of the mucosa at the point of its attachment to one of these tributaries, and thus allow the contrast medium to pass from the pelvis into the junctional venous vessels and thence into [illegible] would

an excellent [illegible] can be obtained by the injection of a mass up the ureter, an observation first made by

Fig. 78 Photomicrograph of neoprene cast [illegible] junctional vessels themselves (for further description see text).

Bowman (1842). The important relation between the development of hydronephrosis and pyelovenous back flow is discussed by Hinman (1945).

Relations of arterial and venous sides of the cortical intertubular capillary network

We have noted in our injected preparations, of both human and animal kidneys, that the arterial and venous sides of the cortical intertubular capillary network bear a constant relation to certain segments of the uriniferous tubules. The distribution of the two sides of this capillary bed may be well seen in a preparation from a kidney injected with masses of different colours via the renal artery and renal vein respectively. The capillaries which are filled by the venous injection mass invest each little columnar unit, or lobulus, composed of an interlobular vein, interlobular artery, the glomeruli of this artery, and their proximal and distal convoluted tubules. On the other hand, the capillaries which are filled by the arterial injection surround parts of the loops of Henle and the collecting tubules which together compose a medullary ray, and are situated in the spaces between adjacent lobuli (Figure 79*a*, *b*). In dual injection preparations the cortex shows areas of [illegible]

with unfilled areas. Sometimes, however, a very free flowing mass, injected via the renal artery, fills not only the capillaries on the arterial side of the cortical intertubular capillary network but, penetrating farther, fills also the capillaries on the venous side, and in such preparations the characteristic distribution cannot be appreciated. Sections of kidneys injected from the venous side alone show particularly well that the glomeruli are embedded in a venous capillary plexus, for the glomeruli are seen as rounded empty spaces which are conspicuous in the filled plexus (Figure [illegible]). It is interesting to compare this figure with the rat [illegible] shows the same empty glomerular s[illegible] In this earlier case (Figure 29*c*) the injection was introduced from the arterial side, and the filling of the venous elements of the cortical intertubular capillary system was effected by reflux through the cortical veins from the vessels of the medullary by-pass.

Tangential sections of a kidney injected from the venous side, such as that illustrated in Figure 79*d*, show a honeycomb pattern. The capillaries of the medullary rays, which are filled in preparations injected from the arterial side, are here empty, and these rays are therefore conspicuous as white spaces in an irregular framework of black, formed by the well-filled venous side of the capillary network which envelops the numerous lobuli. Occasionally, small round empty spaces are seen in the midst of the densely-filled areas;

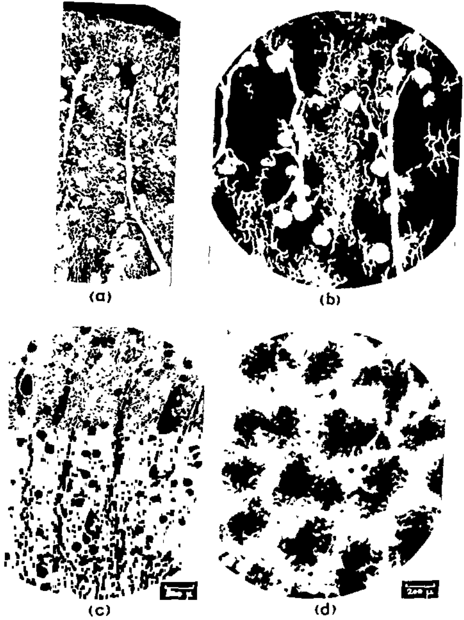

Fig 79 Photomicrographs of sections of human kidneys injected with Indian ink To show distribution of [illegible]

a

these represent unfilled interlobular arteries, running at right angles to the plane of section

Thus, the parts of the nephron which receive blood most rich in oxygen are those which are situated in the medullary ray (parts of the loop of Henle), for the capillaries surrounding these parts of the tubule derive their blood supply directly from the efferent vessels of the cortical glomeruli. On the other hand, the proximal and distal convoluted tubules, adjacent to the Malpighian corpuscle, receive less well oxygenated blood, since the capillaries which surround these parts of the nephron are supplied with blood which has already circulated through the arterial side of the cortical intertubular capillary bed. The distribution of the capillaries of the arterial side of the cortical intertubular capillary bed, in relation to the Malpighian corpuscle and the proximal convoluted tubule, is well seen in Figure 80. In this preparation the injected neoprene has not only filled a cortical glomerulus, its efferent vessel, and a considerable part of the capillary network into which this efferent vessel empties, but it has also forced its way into part of the proximal convolution of the tubule associated with this glomerulus The capillaries filled from the efferent vessel do not surround either the glomerulus or the proximal convoluted tubule, but are situated away from these in the region of a medullary ray.

FIG 80 Photomicrograph of neoprene cast of cortical glomerulus from human kidney The injection mass has ruptured some of the glomerular capillaries and is seen [illegible]

The differences in oxygen tension of the blood supplying different parts of the tubule must clearly be of significance to the functions of these parts.

Moreover, the effects of diffusion gradients must apply no less to the cortical intertubular capillary bed than to capillary beds elsewhere in the body.

It will be appreciated from the above account that the arrangement of the cortical intertubular capillary network depicted in the diagrams of current textbooks is frequently erroneous. For example, the diagram illustrated in Figure 25 gives a wholly false impression of the distribution of the venous elements of the cortical intertubular capillary network.

The superficial veins of the kidney

In examining the kidney of the cat we were immediately impressed by the large venous trunks underlying the capsule. So great a development of the

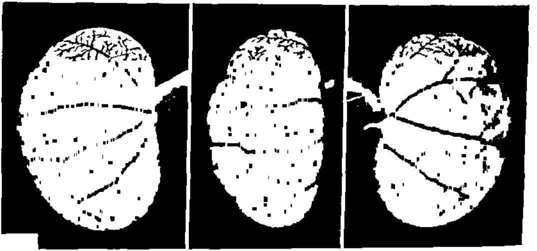

FIG 81 Photographs of the kidney of a cat injected with white neoprene via the renal artery and blue neoprene via the renal vein To show the beautiful pattern of the highly developed system of superficial veins of the kidney of this species of animal See also Figure 26*a*, a photograph of the neoprene cast taken after the kidney had been macerated

superficial elements of the renal venous system was not found in the kidneys of any of the other species of animals examined, though the dog's kidney showed a system somewhat comparable. The external appearance of a cat's kidney after an injection from the venous side was wholly different from that of the kidney of any other animal after a similar injection, and made an exquisitely beautiful picture (Figure 81). The deep venous system of the kidney of the cat is comparable to that of the kidneys of other animals in its general arrangement, but it is noticeable that in both the cat and the dog the vessels composing this system are smaller than they are in the kidneys of animals of other species, which do not show the highly developed system of superficial veins.

In the human kidney the only representatives of the highly developed

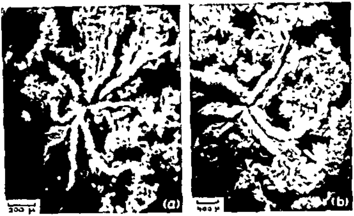

FIG 82 Photomicrographs of stellate veins of human kidneys Neoprene casts, (*a*) from kidney of newborn child, (*b*) from kidney of adult

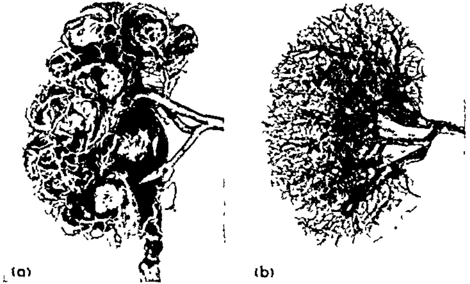

FIG 83 Photographs of celloidin casts of the renal arterial trees of (*a*) a hydronephrotic human kidney, and (*b*) a normal human kidney for comparison Note in the hydronephrotic kidney the reduced peripheral vascular bed, although the main vessels show little if any reduction in calibre (The specimen (*a*) shows, in addition, a cast of the dilated renal pelvis made by means of a ureteric injection of celloidin)

superficial venous system of the cat are the stellate veins. These stout little vessels are aptly named, for they have a truly starlike appearance. Each little group of vessels approaches a common centre where they all bend sharply to penetrate the cortex (Figure 82) before fusing to join an interlobular vein. Occasionally, a small vein from the perinephric tissues joins the centre of one of the little groups of veins.

Hydronephrosis

One further specimen, obtained during the course of our studies on the renal circulation, may be of interest. Figure 83*a* illustrates the vascular pattern of a case of long-standing hydronephrosis in a human subject. It will be noted, by comparison with Figure 83*b* which illustrates a normal kidney, that there is a very great reduction in the smaller elements of the renal arterial tree, although the calibre of the main arteries shows little difference from the normal. We feel that the changes in distribution of the intrarenal blood flow brought about by the development of hydronephrosis offer a promising field for investigation on the lines of the experimental methods used in our studies on the renal circulation.

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